HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Kaletra safely and effectively. See full prescribing information for Kaletra.

Kaletra (lopinavir and ritonavir) Tablet, Film Coated for Oral use
Kaletra (lopinavir and ritonavir) Solution for Oral use
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Dosage and Administration, Pediatric Patients (2.2) 11/2007
Contraindications, Table 3 (4) 11/2007
Contraindications, Table 3 (4) 6/2008
Dosage and Administration, Pediatric Patients (2.2) 6/2008

INDICATIONS AND USAGE

KALETRA is an HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. (1)

DOSAGE AND ADMINISTRATION

Do not use once-daily administration of KALETRA in:

- Therapy-experienced patients (2.1)
- Combination with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir (2.1)
- Pediatric patients (2.2)

Tablets: May be taken with or without food, swallowed whole and not chewed, broken, or crushed. (2)
Oral Solution: Must be taken with food. (2)
ADULT PATIENTS Therapy-Naïve (2.1)

- 400/100 mg (two 200/50 mg tablets or 5 mL oral solution) twice-daily

or

- 800/200 mg (four 200/50 mg tablets or 10 mL oral solution) once-daily.

ADULT PATIENTS Therapy-Experienced (2.1)

- 400/100 mg (two 200/50 mg tablets or 5 mL oral solution) twice-daily

PEDIATRIC PATIENTS (ages 14 days and older) (2.2)

- Twice-daily dose is based on body weight.

Concomitant Therapy in Adults and Pediatric Patients (2.1, 2.2)

- Dose adjustments of KALETRA may be needed when co-administering with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir.

DOSAGE FORMS AND STRENGTHS

- Film-coated tablets: 200 mg lopinavir and 50 mg ritonavir (3)
- Film-coated tablets: 100 mg lopinavir and 25 mg ritonavir (3)
- Oral solution: 80 mg lopinavir and 20 mg ritonavir per milliliter (3)

CONTRAINDICATIONS

Hypersensitivity to KALETRA (e.g., Stevens-Johnson syndrome, erythema multiforme) or any of its ingredients, including ritonavir. (4)
Coadministration with:

- drugs highly dependent on CYP3A for clearance and for which elevated plasma levels may result in serious and/or life-threatening events. (4)
- potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross resistance. (4)

WARNINGS AND PRECAUTIONS

The following have been observed in patients receiving KALETRA:

- Drug Interactions: Consider drug-drug interaction potential to reduce risk of serious or life-threatening adverse reactions. (5.1)
- Pancreatitis: Fatalities have occurred; suspend therapy as clinically appropriate. (5.2)
- Hepatotoxicity: Fatalities have occurred. Monitor liver function before and during therapy, especially in patients with underlying hepatic disease, including hepatitis B and hepatitis C, or marked transaminase elevations. (5.3, 8.6)
- Patients may develop new onset or exacerbations of diabetes mellitus, hyperglycemia (5.4), immune reconstitution syndrome (5.5), redistribution/accumulation of body fat. (5.6)
- Total cholesterol and triglycerides elevations. Monitor prior to therapy and periodically thereafter. (5.7)
- Hemophilia: Spontaneous bleeding may occur, and additional factor VIII may be required. (5.8)

ADVERSE REACTIONS

The most common adverse reactions (> 5%) were diarrhea, nausea, abdominal pain, asthenia, vomiting, headache, and dyspepsia. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Abbott Laboratories at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Coadministration of KALETRA can alter the concentrations of other drugs and other drugs may alter the concentrations of lopinavir. The potential for drug-drug interactions must be considered prior to and during therapy. (4, 5.1, 7, 12.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Physicians are encouraged to register patients in the Antiretroviral Pregnancy Registry by calling 1-800-258-4263. (8.1)
- Pediatric Use: The safety, efficacy, and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 14 days have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 06/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

---

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The following points should be considered when initiating therapy with KALETRA:

- The use of other active agents with KALETRA is associated with a greater likelihood of treatment response *[see Clinical Pharmacology (12.4) and Clinical Studies (14)]*.

- Genotypic or phenotypic testing and/or treatment history should guide the use of KALETRA *[see Clinical Pharmacology (12.4)]*. The number of baseline primary protease inhibitor mutations affects the virologic response to KALETRA *[see Clinical Pharmacology (12.4)]*.
- Once-daily administration of KALETRA is not recommended for therapy-experienced adult patients or any pediatric patients.

2 DOSAGE AND ADMINISTRATION

KALETRA tablets may be taken with or without food. The tablets should be swallowed whole and not chewed, broken, or crushed.

KALETRA oral solution must be taken with food.

2.1 Adult Patients

Therapy-Naïve Patients

- KALETRA tablets 400/100 mg (given as two 200/50 mg tablets) twice-daily taken with or without food.
- KALETRA oral solution 400/100 mg (5 mL) twice-daily taken with food.
- KALETRA tablets 800/200 mg (given as four 200/50 mg tablets) once-daily taken with or without food.
- KALETRA oral solution 800/200 mg (10 mL) once-daily taken with food.

When initiating treatment with KALETRA in therapy-naïve patients, it should be noted the incidence of diarrhea was greater with KALETRA capsules once-daily compared to KALETRA capsules twice-daily in Study 418 (57% vs. 35% - reactions of all grades; 16% vs. 5% - reactions of at least moderate severity) *[See ADVERSE REACTIONS (6.1) and DOSAGE AND ADMINISTRATION (2.1)]*.

Therapy-Experienced Patients

Once-daily administration of KALETRA is not recommended in therapy-experienced patients.

- KALETRA tablets 400/100 mg (given as two 200/50 mg tablets) twice-daily taken with or without food.
- KALETRA oral solution 400/100 mg (5 mL) twice-daily taken with food.

Concomitant Therapy: Efavirenz, nevirapine, (fos)amprenavir or nelfinavir

[See CLINICAL PHARMACOLOGY (12.3) and DRUG INTERACTIONS (7.3)]

KALETRA tablets and oral solution should not be administered as a once-daily regimen in combination with efavirenz, nevirapine, (fos)amprenavir or nelfinavir.

- A dose increase is recommended for all patients who use KALETRA tablets. The recommended dose of KALETRA tablets is 500/125 mg (such as two 200/50 tablets and one 100/25 mg tablet) twice daily in combination with efavirenz, nevirapine, (fos)amprenavir or nelfinavir.
- A dose increase is recommended for all patients who use KALETRA oral solution. The recommended dose of KALETRA oral solution is 533/133 mg (6.5 mL) twice-daily taken with food when used in combination with efavirenz, nevirapine, (fos)amprenavir or nelfinavir.

2.2 Pediatric Patients

KALETRA tablets and oral solution should not be administered once-daily in pediatric patients < 18 years of age.

Healthcare professionals should pay special attention to accurate calculation of the dose of KALETRA, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors, overdose, *[see OVERDOSAGE (10)]* and underdose.

Prescribers should calculate the appropriate dose of KALETRA for each individual child based on body weight (kg) or body surface area (BSA) and should not exceed the recommended adult dose.

Body surface area (BSA) can be calculated as follows:

$$\text{BSA } (m^2) = \sqrt{\frac{\text{Ht (Cm)} \times \text{Wt (kg)}}{3600}}$$

The KALETRA dose can be calculated based on weight or BSA:

Based on Weight:

Patient Weight (kg) × Prescribed lopinavir dose (mg/kg) = Administered lopinavir dose (mg)

Based on BSA:

Patient BSA (m^2) × Prescribed lopinavir dose (mg/m^2) = Administered lopinavir dose (mg)

If KALETRA oral solution is used, the volume (mL) of KALETRA solution can be determined as follows:

Volume of KALETRA solution (mL) = Administered lopinavir dose (mg) ÷ 80 (mg/mL)

The dose of the oral solution should be administered using a calibrated dosing syringe.

Before prescribing KALETRA 100/25 mg tablets, children should be assessed for the ability to swallow intact tablets. If a child is unable to reliably swallow a KALETRA tablet, the KALETRA oral solution formulation should be prescribed.

14 Days to 6 Months:

In pediatric patients 14 days to 6 months of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution is 16/4 mg/kg or 300/75 mg/m^2 twice daily. Prescribers should calculate the appropriate dose based on body weight or body surface area.

Because no data exists for dosage when administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir, it is recommended that KALETRA not be administered in combination with these drugs in patients < 6 months of age.

6 Months to 18 Years:

Without Concomitant Efavirenz, Nevirapine, (Fos)amprenavir or Nelfinavir

In children 6 months to 18 years of age, the recommended dosage of lopinavir/ritonavir using KALETRA oral solution without concomitant efavirenz, nevirapine, (fos)amprenavir, or nelfinavir is 230/57.5 mg/m^2 given twice daily, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage of lopinavir/ritonavir for patients < 15 kg is 12/3 mg/kg given twice daily and the dosage for patients ≥ 15 kg to 40 kg is 10/2.5 mg/kg given twice daily.

Table 1 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on body weight or body surface area for KALETRA tablets.

Table 1. Pediatric Dosing Recommendations for Patients 6 Months to 18 Years of Age Based on Body Weight or Body Surface Area for KALETRA Tablets Without Concomitant Efavirenz, Nevirapine, (Fos)amprenavir, or Nelfinavir

Body Weight (kg)	Body Surface Area (m^2)*	Recommended number of 100/25 mg Tablets Twice-Daily
15 to 25	≥0.6 to < 0.9	2
>25 to 35	≥0.9 to < 1.4	3
>35	≥1.4	4 (or two 200/50 mg tablets)

* KALETRA oral solution is available for children with a BSA less than 0.6 m^2 or those who are unable to reliably swallow a tablet.

Concomitant Therapy: Efavirenz, Nevirapine, (Fos)amprenavir, or Nelfinavir

A dose increase of KALETRA to 300/75 mg/m^2 is needed when co-administered with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir in children (both treatment-naïve and treatment-experienced) 6 months to 18 years of age, not to exceed the recommended adult dose. If weight-based dosing is preferred, the recommended dosage for patients <15 kg is 13/3.25 mg/kg given twice daily and the dosage for patients >15 kg to 45 kg is 11/2.75 mg/kg given twice daily.

Table 2 provides the dosing recommendations for pediatric patients 6 months to 18 years of age based on body weight or body surface area for KALETRA tablets when given in combination with efavirenz, nevirapine, (fos)amprenavir, or nelfinavir.

Table 2. Pediatric Dosing Recommendations for Patients 6 Months to 18 Years of Age Based on Body Weight or Body Surface Area for KALETRA Tablets With Concomitant Efavirenz†, Nevirapine, (Fos)amprenavir† or Nelfinavir†

Body Weight (kg)	Body Surface Area (m^2)*	Recommended number of 100/25 mg Tablets Twice-Daily
15 to 20	≥0.6 to < 0.8	2
>20 to 30	≥0.8 to < 1.2	3
>30 to 45	≥1.2 to <1.7	4 (or two 200/50 mg tablets)
>45	≥1.7	4 or 6 (or two or three 200/50 mg tablets) See Dosage and Administration, Adult Patients (2.1)

* KALETRA oral solution is available for children with a BSA less than 0.6 m^2 or those who are unable to reliably swallow a tablet.

† Please refer to the individual product labels for appropriate dosing in children.

3 DOSAGE FORMS AND STRENGTHS

- **KALETRA Tablets, 200 mg lopinavir/50 mg ritonavir**

Yellow, film-coated, ovaloid tablets debossed with the corporate Abbott “A” logo and the Abbo-Code KA providing 200 mg lopinavir/50 mg ritonavir.

- **KALETRA Tablets, 100 mg lopinavir/25 mg ritonavir**

Pale yellow, film-coated, ovaloid tablets debossed with the corporate Abbott “A” logo and the Abbo-Code KC providing 100 mg lopinavir/25 mg ritonavir.

- **KALETRA Oral Solution**

Light yellow to orange colored liquid containing 400 mg lopinavir/100 mg ritonavir per 5 mL (80 mg lopinavir/20 mg ritonavir per mL).

4 CONTRAINDICATIONS

- KALETRA is contraindicated in patients with previously demonstrated clinically significant hypersensitivity (e.g., Stevens-Johnson syndrome, erythema multiforme) to any of its ingredients, including ritonavir.
- Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions.
- Co-administration of KALETRA is contraindicated with potent CYP3A inducers where significantly reduced lopinavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance and cross-resistance. These drugs are listed in Table 3.

Table 3. Drugs That Are Contraindicated With KALETRA

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA	Clinical comments:
Antimycobacterial	Rifampin	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents. *[see DRUG INTERACTIONS (7)]*
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI motility agent	Cisapride	Potential for cardiac arrhythmias.
Herbal Products	St Johns wort (hypericum perforatum)	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Neuroleptic	Pimozide	Potential for cardiac arrhythmias.
Sedative/Hypnotics	Triazolam; orally administered midazolam[a]	Prolonged or increased sedation or respiratory depression.

[a] *See Drug Interactions, Table 9 for parenterally administered midazolam*

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

See Tables 3 and 9 for listing of drugs that are contraindicated for use with KALETRA due to potentially life-threatening adverse events, significant drug interactions, or loss of virologic activity. *[see CONTRAINDICATIONS (4) and DRUG INTERACTIONS (7)]*.

5.2 Pancreatitis

Pancreatitis has been observed in patients receiving KALETRA therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations are a risk factor for development of pancreatitis *[See WARNINGS AND PRECAUTIONS (5.7)]*. Patients with advanced HIV-1 disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during KALETRA therapy.

Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate.

5.3 Hepatotoxicity

Patients with underlying hepatitis B or C or marked elevations in transaminase prior to treatment may be at increased risk for developing or worsening of transaminase elevations or hepatic decompensation with use of KALETRA.

There have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV-1 disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with KALETRA therapy has not been established.

Appropriate laboratory testing should be conducted prior to initiating therapy with KALETRA and patients should be monitored closely during treatment. Increased AST/ALT monitoring should be

considered in the patients with underlying chronic hepatitis or cirrhosis, especially during the first several months of KALETRA treatment. *[See USE IN SPECIFIC POPULATIONS (8.6)]*

5.4 Diabetes Mellitus/Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-marketing surveillance in HIV-1 infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including KALETRA. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis) which may necessitate further evaluation and treatment.

5.6 Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

5.7 Lipid Elevations

Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides *[See ADVERSE REACTIONS (6.1)]*. Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate, taking into account any potential drug-drug interactions

with KALETRA and HMG-CoA reductase inhibitors. *[See CONTRAINDICATIONS (4) and DRUG INTERACTIONS (7.3)]*

5.8 Patients with Hemophilia

There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

5.9 Resistance/Cross-resistance

Because the potential for HIV cross-resistance among protease inhibitors has not been fully explored in KALETRA-treated patients, it is unknown what effect therapy with KALETRA will have on the activity of subsequently administered protease inhibitors. *[See CLINICAL PHARMACOLOGY (12.4)]*

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling.

- Drug Interactions *[see WARNINGS AND PRECAUTIONS (5.1)]*
- Pancreatitis *[see WARNINGS AND PRECAUTIONS (5.2)]*
- Hepatotoxicity *[see WARNINGS AND PRECAUTIONS (5.3)]*

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adults - Clinical Trials Experience

The safety profile of KALETRA in adults is primarily based on 891 HIV-1 infected patients in clinical trials.

The most common adverse reaction was diarrhea, which was generally of mild to moderate severity. The incidence of diarrhea was greater for KALETRA capsules once-daily compared to KALETRA capsules twice-daily in Study 418 *[See Table 4]*. Rates of discontinuation of randomized therapy due to adverse reactions were 3.4% in KALETRA-treated and 3.7% in nelfinavir-treated patients in Study 863.

Treatment-emergent clinical adverse reactions of moderate or severe intensity in ≥ 2% of patients treated with combination therapy for up to 48 weeks (Study 863 and 418) and for up to 360 weeks (Study 720) are presented in Table 4 (treatment-naïve patients) and Table 5 (protease inhibitor experienced patients).

Table 4. Percentage of Adult Patients with Selected Treatment-Emergent[1] Adverse Reactions of Moderate or Severe Intensity Reported in ≥ 2% of Adult Antiretroviral-Naïve Patients

	Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)
	KALETRA 400/100 mg BID + d4T + 3TC (N = 326)	Nelfinavir 750 mg TID + d4T + 3TC (N = 327)	KALETRA 800/200 mg QD + TDF + FTC (N = 115)	KALETRA 400/100 mg BID + TDF + FTC (N = 75)	KALETRA BID[2] + d4T + 3TC (N = 100)
Body as a Whole					
Abdominal Pain	4%	3%	3%	3%	11%
Asthenia	4%	3%	0%	0%	9%
Headache	2%	2%	3%	3%	6%
Cardiovascular System					
Vein distended	0%	0%	0%	0%	3%
Digestive System					
Diarrhea	16%	17%	16%	5%	28%
Nausea	7%	5%	9%	8%	16%
Vomiting	2%	2%	3%	4%	6%
Dyspepsia	2%	< 1%	0%	1%	6%
Flatulence	2%	1%	2%	1%	4%
Anorexia	1%	< 1%	< 1%	1%	2%
Metabolic and Nutritional					
Weight loss	1%	< 1%	0%	0%	2%
Musculoskeletal					
Myalgia	1%	1%	0%	0%	2%
Nervous System					
Insomnia	2%	1%	0%	0%	3%
Paresthesia	1%	1%	0%	0%	2%
Depression	1%	2%	1%	0%	0%
Libido decreased	< 1%	< 1%	0%	1%	2%
Respiratory					

Bronchitis	0%	0%	0%	0%	2%
Skin and Appendages					
Rash	1%	2%	1%	0%	5%
Urogenital					
Hypogonadism male	0%	0%	0%	0%	2%
Amenorrhea	0%	0%	4.5%	0%	0%

1 Includes adverse reactions of possible or probable relationship to study drug.

2 Includes adverse reaction data from dose group I (200/100 mg BID [N = 16] and 400/100 mg BID [N = 16]) and dose group II (400/100 mg BID [N = 35] and 400/200 mg BID [N = 33]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.

Definitions: d4T = Stavudine; 3TC = Lamivudine; TDF = Tenofovir Disoproxil Fumarate; FTC = Emtricitabine

Table 5. Percentage of Adult Patients with Selected Treatment-Emergent[1] Adverse Reactions of Moderate or Severe Intensity Reported in ≥ 2% of Adult Protease Inhibitor-Experienced Patients

	Study 888 (48 Weeks)		Study 957[2] and Study 765[3] (84-144 Weeks)
	KALETRA 400/100 mg BID + NVP + NRTIs (N = 148)	Investigator-selected protease inhibitor(s) + NVP + NRTIs (N = 140)	KALETRA BID + NNRTI + NRTIs (N = 127)
Body as a Whole			
Asthenia	3%	6%	9%
Abdominal Pain	2%	2%	4%
Fever	2%	1%	2%
Headache	2%	3%	2%
Chills	2%	0%	0%
Cardiovascular			
Hypertension	0%	0%	2%
Digestive System			
Diarrhea	7%	9%	23%
Nausea	7%	16%	5%
Vomiting	4%	12%	2%
Dyspepsia	1%	1%	2%
Flatulence	1%	2%	2%
Dysphagia	2%	1%	0%
Anorexia	1%	3%	0%

Metabolic and Nutritional			
Weight loss	0%	1%	3%
Musculoskeletal			
Myalgia	1%	1%	2%
Nervous System			
Depression	1%	2%	2%
Paresthesia	1%	0%	2%
Insomnia	0%	2%	2%
Skin and Appendages			
Rash	2%	1%	2%

1 Includes adverse reactions of possible or probable relationship to study drug.

2 Includes adverse reaction data from patients receiving 400/100 mg BID (n = 29) or 533/133 mg BID (n = 28) for 84 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.

3 Includes adverse reaction data from patients receiving 400/100 mg BID (n = 36) or 400/200 mg BID (n = 34) for 144 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.

Definitions: NVP = Nevirapine; NRTI = Nucleoside Reverse Transcriptase Inhibitors; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitors

Less Common Adverse Reactions

Treatment-emergent adverse reactions occurring in less than 2% of adult patients receiving KALETRA in the clinical trials supporting approval and of at least moderate intensity are listed below by body system.

Body as a Whole

Allergic reaction, back pain, chest pain, chest pain substernal, cyst, drug interaction, drug level increased, face edema, flu syndrome, hypertrophy, infection bacterial, malaise, neoplasm, and viral infection.

Cardiovascular System

Atrial fibrillation, cerebral infarct, deep thrombophlebitis, deep vein thrombosis, migraine, myocardial infarct, palpitation, postural hypotension, thrombophlebitis, varicose vein, and vasculitis.

Digestive System

Cholangitis, cholecystitis, constipation, dry mouth, enteritis, enterocolitis, eructation, esophagitis, fecal incontinence, gastritis, gastroenteritis, hemorrhagic colitis, hepatitis, hepatomegaly, increased

appetite, jaundice, liver fatty deposit, liver tenderness, mouth ulceration, pancreatitis, periodontitis, sialadenitis, stomatitis, and ulcerative stomatitis.

Endocrine System

Cushing's syndrome, diabetes mellitus, and hypothyroidism.

Hemic and Lymphatic System

Anemia, leukopenia, and lymphadenopathy.

Metabolic and Nutritional Disorders

Avitaminosis, dehydration, edema, glucose tolerance decreased, lactic acidosis, obesity, peripheral edema, and weight gain.

Musculoskeletal System

Arthralgia, arthrosis, bone necrosis, joint disorder, and myasthenia.

Nervous System

Abnormal dreams, agitation, amnesia, anxiety, apathy, ataxia, confusion, convulsion, dizziness, dyskinesia, emotional lability, encephalopathy, extrapyramidal syndrome, facial paralysis, hypertonia, nervousness, neuropathy, peripheral neuritis, somnolence, thinking abnormal, tremor, and vertigo.

Respiratory System

Asthma, cough increased, dyspnea, lung edema, pharyngitis, rhinitis, and sinusitis.

Skin and Appendages

Acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, maculopapular rash, nail disorder, pruritis, seborrhea, skin benign neoplasm, skin discoloration, skin striae, skin ulcer, and sweating.

Special Senses

Abnormal vision, eye disorder, otitis media, taste loss, taste perversion, and tinnitus.

Urogenital System

Abnormal ejaculation, breast enlargement, gynecomastia, impotence, kidney calculus, nephritis, and urine abnormality.

Laboratory Abnormalities

The percentages of adult patients treated with combination therapy with Grade 3-4 laboratory abnormalities are presented in Table 6 (treatment-naïve patients) and Table 7 (treatment-experienced patients).

Table 6. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Antiretroviral-naïve Patients

		Study 863 (48 Weeks)		Study 418 (48 Weeks)		Study 720 (360 Weeks)
Variable	Limit[1]	KALETRA 400/100 mg BID + d4T +3TC (N = 326)	Nelfinavir 750 mg TID + d4T + 3TC (N = 327)	KALETRA 800/200 mg QD + TDF + FTC (N = 115)	KALETRA 400/100 mg BID + TDF + FTC (N = 75)	KALETRA BID[2] + d4T + 3TC (N = 100)
Chemistry	**High**					
Glucose	> 250 mg/dL	2%	2%	3%	1%	4%
Uric Acid	> 12 mg/dL	2%	2%	0%	3%	5%
SGOT/ AST	> 180 U/L	2%	4%	5%	3%	10%
SGPT/ ALT	>215 U/L	4%	4%	4%	3%	11%
GGT	>300 U/L	N/A	N/A	N/A	N/A	10%
Total Cholesterol	>300 mg/dL	9%	5%	3%	3%	27%
Triglycerides	>750 mg/dL	9%	1%	5%	4%	29%
Amylase	>2 x ULN	3%	2%	7%	5%	4%
Hematology	**Low**					
Neutrophils	<0.75 x 10^9/L	1%	3%	5%	1%	5%

1 ULN = upper limit of the normal range; N/A = Not Applicable.

2 Includes adverse event data from dose group I (200/100 mg BID [N = 16] and 400/100 mg BID [N = 16]) and dose group II (400/100 mg BID [N = 35] and 400/200 mg BID [N = 33]). Within dosing groups, moderate to severe nausea of probable/possible relationship to KALETRA occurred at a higher rate in the 400/200 mg dose arm compared to the 400/100 mg dose arm in group II.

Table 7. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% of Adult Protease Inhibitor-experienced Patients

Variable	Limit[1]	Study 888 (48 Weeks) KALETRA 400/100 mg BID + NVP + NRTIs (N = 148)	Study 888 (48 Weeks) Investigator-selected protease inhibitor(s) + NVP + NRTIs (N = 140)	Study 957[2] and Study 765[3](84-144 Weeks) KALETRA BID + NNRTI + NRTIs (N = 127)
Chemistry	**High**			
Glucose	>250 mg/dL	1%	2%	5%
Total Bilirubin	>3.48 mg/dL	1%	3%	1%
SGOT/AST	>180 U/L	5%	11%	8%
SGPT/ALT	>215 U/L	6%	13%	10%
GGT	>300 U/L	N/A	N/A	29%
Total Cholesterol	>300 mg/dL	20%	21%	39%
Triglycerides	>750 mg/dL	25%	21%	36%
Amylase	>2 x ULN	4%	8%	8%
Chemistry	**Low**			
Inorganic Phosphorus	<1.5 mg/dL	1%	0%	2%
Hematology	**Low**			
Neutrophils	<0.75 x 10^9/L	1%	2%	4%

1 ULN = upper limit of the normal range; N/A = Not Applicable.

2 Includes clinical laboratory data from patients receiving 400/100 mg BID (n = 29) or 533/133 mg BID (n = 28) for 84 weeks. Patients received KALETRA in combination with NRTIs and efavirenz.

3 Includes clinical laboratory data from patients receiving 400/100 mg BID (n = 36) or 400/200 mg BID (n = 34) for 144 weeks. Patients received KALETRA in combination with NRTIs and nevirapine.

6.2 Pediatric Patients - Clinical Trials Experience

KALETRA oral solution dosed up to 300/75 mg/m^2 has been studied in 100 pediatric patients 6 months to 12 years of age. The adverse reaction profile seen during Study 940 was similar to that for adult patients.

Dysgeusia (22%), vomiting (21%), and diarrhea (12%) were the most common adverse reactions of any severity reported in pediatric patients treated with combination therapy for up to 48 weeks in Study 940. A total of 8 patients experienced adverse reactions of moderate to severe intensity. The adverse reactions meeting these criteria and reported for the 8 subjects include: hypersensitivity (characterized by fever, rash and jaundice), pyrexia, viral infection, constipation, hepatomegaly, pancreatitis, vomiting, alanine aminotransferase increased, dry skin, rash, and dysgeusia. Rash was the only event of those listed that occurred in 2 or more subjects (N = 3).

KALETRA oral solution dosed at 300/75 mg/m^2 has been studied in 31 pediatric patients 14 days to 6 months of age. The adverse reaction profile in Study 1030 was similar to that observed in older children and adults. No adverse reaction was reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included decreased neutrophil count (N=3), anemia (N=2), high potassium (N=2), and low sodium (N=2).

KALETRA oral solution and soft gelatin capsules dosed at higher than recommended doses including 400/100 mg/m^2 (without concomitant NNRTI) and 480/120 mg/m^2 (with concomitant NNRTI) have been studied in 26 pediatric patients 7 to 18 years of age in Study 1038. Patients also had saquinavir mesylate added to their regimen at Week 4. Rash (12%), blood cholesterol abnormal (12%) and blood triglycerides abnormal (12%) were the only adverse reactions reported in greater than 10% of subjects. Adverse drug reactions of moderate to severe intensity occurring in 2 or more subjects included rash (N=3), blood triglycerides abnormal (N=3), and electrocardiogram QT prolonged (N=2). Both subjects with QT prolongation had additional predisposing conditions such as electrolyte abnormalities, concomitant medications, or pre-existing cardiac abnormalities.

Laboratory Abnormalities

The percentages of pediatric patients treated with combination therapy including KALETRA with Grade 3-4 laboratory abnormalities are presented in Table 8.

Table 8. Grade 3-4 Laboratory Abnormalities Reported in ≥ 2% Pediatric Patients in Study 940

Variable	Limit[1]	KALETRA BID+ RTIs (N = 100)
Chemistry	**High**	
Sodium	> 149 mEq/L	3%
Total Bilirubin	≥ 3.0 x ULN	3%
SGOT/AST	> 180 U/L	8%
SGPT/ALT	> 215 U/L	7%

Total Cholesterol	> 300 mg/dL	3%
Amylase	> 2.5 x ULN	7%[2]
Chemistry	**Low**	
Sodium	< 130 mEq/L	3%
Hematology	**Low**	
Platelet Count	< 50 x 10^9/L	4%
Neutrophils	< 0.40 x 10^9/L	2%

1 ULN = upper limit of the normal range.

2 Subjects with Grade 3-4 amylase confirmed by elevations in pancreatic amylase.

6.3 Postmarketing Experience

The following adverse reactions have been reported during postmarketing use of KALETRA. Because these reactions are reported voluntarily from a population of unknown size, it is not possible to reliably estimate their frequency or establish a causal relationship to KALETRA exposure.

Body as a Whole

Redistribution/accumulation of body fat has been reported *[See WARNINGS AND PRECAUTIONS (5.6)]*.

Cardiovascular

Bradyarrhythmias.

Skin and Appendages

Stevens Johnson Syndrome and erythema multiforme.

7 DRUG INTERACTIONS

See also CONTRAINDICATIONS (4), CLINICAL PHARMACOLOGY (12.3)

7.1 Potential for KALETRA to Affect Other Drugs

Lopinavir/ritonavir is an inhibitor of CYP3A and may increase plasma concentrations of agents that are primarily metabolized by CYP3A. Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (> 3-fold) when co-administered with KALETRA. Thus, co-administration of KALETRA with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated

with serious and/or life-threatening events is contraindicated. Co-administration with other CYP3A substrates may require a dose adjustment or additional monitoring as shown in Table 9.

Additionally, KALETRA induces glucuronidation.

7.2 Potential For Other Drugs To Affect Lopinavir

Lopinavir/ritonavir is a CYP3A substrate; therefore, drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce KALETRA's therapeutic effect. Although not observed in the KALETRA/ketoconazole drug interaction study, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

7.3 Established and Other Potentially Significant Drug Interactions

Table 9 provides a listing of established or potentially clinically significant drug interactions. Alteration in dose or regimen may be recommended based on drug interaction studies or predicted interaction. *[See CLINICAL PHARMACOLOGY (12.3) for magnitude of interaction]*

Table 9. Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
		HIV-1 Antiviral Agents
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz*, nevirapine*	↓ lopinavir	KALETRA dose increase is recommended in all patients *[See DOSAGE AND ADMINISTRATION (2.1) and CLINICAL PHARMACOLOGY (12.3)]*. Increasing the dose of KALETRA tablets to 500/125 mg (given as two 200/50 tablets and one 100/25 mg tablet) twice daily co-administered with efavirenz resulted in similar lopinavir concentrations compared to KALETRA tablets 400/100 mg (given as two 200/50 mg tablets) twice daily without efavirenz. Increasing the dose of KALETRA tablets to 600/150 mg (given as three 200/50 mg tablets) twice-daily co-administered with efavirenz resulted in significantly higher lopinavir plasma concentrations compared to KALETRA tablets 400/100 mg twice-daily without efavirenz. KALETRA should not be administered once-daily in combination with efavirenz or nevirapine. *[See DOSAGE AND ADMINISTRATION (2.1) and CLINICAL PHARMACOLOGY (12.3)]*.

Non-nucleoside Reverse Transcriptase Inhibitor: delavirdine	↑ lopinavir	Appropriate doses of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		KALETRA tablets can be administered simultaneously with didanosine without food. For KALETRA oral solution, it is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA oral solution (given with food).
Nucleoside Reverse Transcriptase Inhibitor: tenofovir	↑ tenofovir	KALETRA increases tenofovir concentrations. The mechanism of this interaction is unknown. Patients receiving KALETRA and tenofovir should be monitored for adverse reactions associated with tenofovir.
Nucleoside Reverse Transcriptase Inhibitor: abacavir zidovudine	↓ abacavir ↓ zidovudine	KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.
HIV-1 Protease Inhibitor: amprenavir*	↑ amprenavir ↓ lopinavir	KALETRA should not be administered once-daily in combination with amprenavir. *[See DOSAGE AND ADMINISTRATION (2.1)]*.
HIV-1 Protease Inhibitor: fosamprenavir/ritonavir	↓ amprenavir ↓ lopinavir	An increased rate of adverse reactions has been observed with co-administration of these medications. Appropriate doses of the combinations with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: indinavir*	↑ indinavir	Decrease indinavir dose to 600 mg BID, when co-administered with KALETRA 400/100 mg BID *[See CLINICAL PHARMACOLOGY (12.3)]*. KALETRA once-daily has not been studied in combination with indinavir.
HIV-1 Protease Inhibitor: nelfinavir*	↑ nelfinavir ↑ M8 metabolite of nelfinavir ↓ lopinavir	KALETRA should not be administered once-daily in combination with nelfinavir. *[See DOSAGE AND ADMINISTRATION (2.1) and CLINICAL PHARMACOLOGY (12.3)]*.
HIV-1 Protease Inhibitor: ritonavir*	↑ lopinavir	Appropriate doses of additional ritonavir in combination with KALETRA with respect to safety and efficacy have not been established.
HIV-1 Protease Inhibitor: saquinavir*	↑ saquinavir	The saquinavir dose is 1000 mg BID, when co-administered with KALETRA 400/100 mg BID. KALETRA once-daily has not been studied in combination with saquinavir.
HIV-1 Protease Inhibitor: tipranavir	↓ lopinavir AUC and	KALETRA should not be administered with tipranavir (500 mg twice-daily) co-administered with ritonavir (200 mg

	C_{min}	twice-daily).
HIV CCR5 – antagonist: Maraviroc	↑ maraviroc	Concurrent administration of maraviroc with KALETRA will increase plasma levels of maraviroc. When co-administered, patients should receive 150 mg BID of maraviroc. For further details see complete prescribing information for Selzentry® (maraviroc).
		Other Agents
Antiarrhythmics: amiodarone, bepridil, lidocaine (systemic), and quinidine	↑ antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when co-administered with KALETRA.
Anticancer Agents: vincristine vinblastine	↑ anticancer agents	Concentrations of vincristine or vinblastine may be increased when co-administered with lopinavir/ritonavir (KALETRA) resulting in the potential for increased adverse events usually associated with these anticancer agents. Consideration should be given to temporarily withholding the ritonavir-containing antiretroviral regimen in patients who develop significant hematologic or gastrointestinal side effects when lopinavir/ritonavir (KALETRA) is administered concurrently with vincristine or vinblastine. If the antiretroviral regimen must be withheld for a prolonged period, consideration should be given to initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ lopinavir ↓ phenytoin	KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly and should be used with caution. KALETRA should not be administered once-daily in combination with carbamazepine, phenobarbital, or phenytoin. In addition, co-administration of phenytoin and KALETRA may cause decreases in steady-state phenytoin concentrations. Phenytoin levels should be monitored when co-administering with KALETRA.
Antidepressant: bupropion	↓ bupropion ↓ active metabolite,	Concurrent administration of bupropion with KALETRA may decrease plasma levels of both bupropion and its active

	hydroxybupropion	metabolite (hydroxybupropion). Patients receiving concurrent KALETRA and bupropion concurrently should be monitored for an adequate clinical response to bupropion.
Antidepressant: trazodone	↑ trazodone	Concomitant use of trazodone and KALETRA may increase concentrations of trazodone. Adverse reactions of nausea, dizziness, hypotension and syncope have been observed following co-administration of trazodone and ritonavir. If trazodone is used with a CYP3A4 inhibitor such as ritonavir, the combination should be used with caution and a lower dose of trazodone should be considered.
Anti-infective: clarithromycin	↑ clarithromycin	For patients with renal impairment, the following dosage adjustments should be considered: • For patients with CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. • For patients with CL_{CR} < 30 mL/min the dose of clarithromycin should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungals: ketoconazole*, itraconazole, voriconazole	↑ ketoconazole ↑ itraconazole ↓ voriconazole	High doses of ketoconazole (>200 mg/day) or itraconazole (> 200 mg/day) are not recommended. Co-administration of voriconazole with KALETRA has not been studied. However, a study has been shown that administration of voriconazole with ritonavir 100 mg every 12 hours decreased voriconazole steady-state AUC by an average of 39%; therefore, co-administration of KALETRA and voriconazole may result in decreased voriconazole concentrations and the potential for decreased voriconazole effectiveness and should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Otherwise, alternative antifungal therapies should be considered in these patients.
Antimycobacterial: rifabutin*	↑ rifabutin and rifabutin metabolite	Dosage reduction of rifabutin by at least 75% of the usual dose of 300 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse reactions is warranted in patients receiving the combination. Further dosage reduction of rifabutin may be necessary.
Antimycobacterial: rifampin	↓ lopinavir	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors

		or other co-administered antiretroviral agents. A study evaluated combination of rifampin 600 mg QD, with KALETRA 800/200 mg BID or KALETRA 400/100 mg + ritonavir 300 mg BID. Pharmacokinetic and safety results from this study do not allow for a dose recommendation. Nine subjects (28%) experienced a ≥ grade 2 increase in ALT/AST, of which seven (21%) prematurely discontinued study per protocol. Based on the study design, it is not possible to determine whether the frequency or magnitude of the ALT/AST elevations observed is higher than what would be seen with rifampin alone. *[See CLINICAL PHARMACOLOGY (12.3) for magnitude of interaction]*.
Antiparasitic: atovaquone	↓ atovaquone	Clinical significance is unknown; however, increase in atovaquone doses may be needed.
Benzodiazepines: parenterally administered midazolam	↑ midazolam	Midazolam is extensively metabolized by CYP3A4. Increases in the concentration of midazolam are expected to be significantly higher with oral than parenteral administration. Therefore, KALETRA should not be given with orally administered midazolam *[see Contraindications (4)]*. If KALETRA is coadministered with parenteral midazolam, close clinical monitoring for respiratory depression and/or prolonged sedation should be exercised and dosage adjustment should be considered.
Calcium Channel Blockers, dihydropyridine: e.g., felodipine, nifedipine, nicardipine	↑ dihydropyridine calcium channel blockers	Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroid: dexamethasone	↓ lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
disulfiram/metronidazole		KALETRA oral solution contains alcohol, which can produce disulfiram-like reactions when co-administered with disulfiram or other drugs that produce this reaction (e.g., metronidazole).
PDE5 inhibitors: sildenafil, tadalafil, vardenafil	↑ sildenafil ↑ tadalafil ↑ vardenafil	Particular caution should be used when prescribing sildenafil, tadalafil, or vardenafil in patients receiving KALETRA. Co-administration of KALETRA with these drugs is expected to substantially increase their concentrations and may result in an increase in associated adverse reactions including hypotension, syncope, visual changes

		and prolonged erection. It is recommended not to exceed the following doses: • Sildenafil: 25 mg every 48 hours • Tadalafil: 10 mg every 72 hours • Vardenafil: 2.5 mg every 72 hours
HMG-CoA Reductase Inhibitors: atorvastatin rosuvastatin	↑ atorvastatin ↑ rosuvastatin	Use lowest possible dose of atorvastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
Immunosuppressants: cyclosporine, tacrolimus, rapamycin	↑ immunosuppressants	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Inhaled Steroid: fluticasone	↑ fluticasone	Concomitant use of fluticasone propionate and KALETRA may increase plasma concentrations of fluticasone propionate, resulting in significantly reduced serum cortisol concentrations. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported during post-marketing use in patients receiving ritonavir and inhaled or intranasally administered fluticasone propionate. Co-administration of fluticasone propionate and KALETRA is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effect.
Narcotic Analgesic: methadone*	↓ methadone	Dosage of methadone may need to be increased when co-administered with KALETRA.
Contraceptive: ethinyl estradiol*	↓ ethinyl estradiol	Because contraceptive steroid concentrations may be altered when KALETRA is co-administered with oral contraceptives or with the contraceptive patch, alternative methods of nonhormonal contraception are recommended.

* *See CLINICAL PHARMACOLOGY (12.3)* for Magnitude of Interaction.

7.4 Drugs with No Observed or Predicted Interactions with KALETRA

Drug interaction studies reveal no clinically significant interaction between KALETRA and desipramine (CYP2D6 probe), pravastatin, stavudine, lamivudine, omeprazole or ranitidine.

Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluvastatin, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluconazole.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rats at the toxic doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice-daily). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal Day 21) occurred.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage. Based on AUC measurements, the drug exposures in rabbits at the toxic doses were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg twice-daily). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiretroviral Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

8.3 Nursing Mothers

The Centers for Disease Control and Prevention recommend that HIV-1 infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV-1. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV-1 transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving KALETRA.

8.4 Pediatric Use

The safety, efficacy, and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 14 days have not been established. KALETRA once-daily has not been evaluated in pediatric patients.

An open-label, multi-center, dose-finding trial was performed to evaluate the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL at a dose of with 300/75 mg/m^2 twice daily plus two NRTIs in HIV-infected infants ≥14 days and < 6 months of age. Results revealed that infants younger than 6 months of age generally had lower lopinavir AUC_{12} than older children (6 months to 12 years of age), however, despite the lower lopinavir drug exposure observed, antiviral activity was demonstrated as reflected in the proportion of subjects who achieved HIV-RNA <400 copies/mL at Week 24 *[see ADVERSE REACTIONS (6.2), CLINICAL PHARMACOLOGY (12.3), CLINICAL STUDIES (14.4)]*.

Safety and efficacy in pediatric patients > 6 months of age was demonstrated in a clinical trial in 100 patients. The clinical trial was an open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety, and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naïve and experienced pediatric patients ages 6 months to 12 years. Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m^2 oral solution twice-daily regimen without nevirapine and the 300/75 mg/m^2 oral solution twice-daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice-daily regimen (without nevirapine) *[see ADVERSE REACTIONS (6.2), CLINICAL PHARMACOLOGY (12.3), CLINICAL STUDIES (14.4)]*.

A prospective multicenter, open-label trial evaluated the pharmacokinetic profile, tolerability, safety and efficacy of high-dose KALETRA with or without concurrent NNRTI therapy (Group 1: 400/100 mg/m^2 twice daily + ≥ 2 NRTIs; Group 2: 480/120 mg/m^2 twice daily + ≥ 1 NRTI + 1 NNRTI) in children and adolescents ≥ 2 years to < 18 years of age who had failed prior therapy. Patients also had saquinavir mesylate added to their regimen. This strategy was intended to assess whether higher than approved doses of KALETRA could overcome protease inhibitor cross-resistance. High doses of KALETRA exhibited a safety profile similar to those observed in previous trials; changes in HIV-1 RNA were less than anticipated; three patients had HIV-1 RNA <400 copies/mL at Week 48. CD4+ cell count increases were noted in the eight patients who remained on treatment for 48 weeks, *[see ADVERSE REACTIONS (6.2), CLINICAL PHARMACOLOGY (12.3)]*.

8.5 Geriatric Use

Clinical studies of KALETRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of KALETRA in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased *[See WARNINGS AND PRECAUTIONS (5.3) and CLINICAL PHARMACOLOGY (12.3)]*.

10 OVERDOSAGE

Overdoses with KALETRA oral solution have been reported. One of these reports described fatal cardiogenic shock in a 2.1 kg infant who received a single dose of 6.5 mL of KALETRA oral solution nine days prior. However, a causal relationship between the overdose and the outcome could not be established. Healthcare professionals should be aware that KALETRA oral solution is highly concentrated and therefore, should pay special attention to accurate calculation of the dose of KALETRA, transcription of the medication order, dispensing information and dosing instructions to minimize the risk for medication errors and overdose. This is especially important for infants and young children.

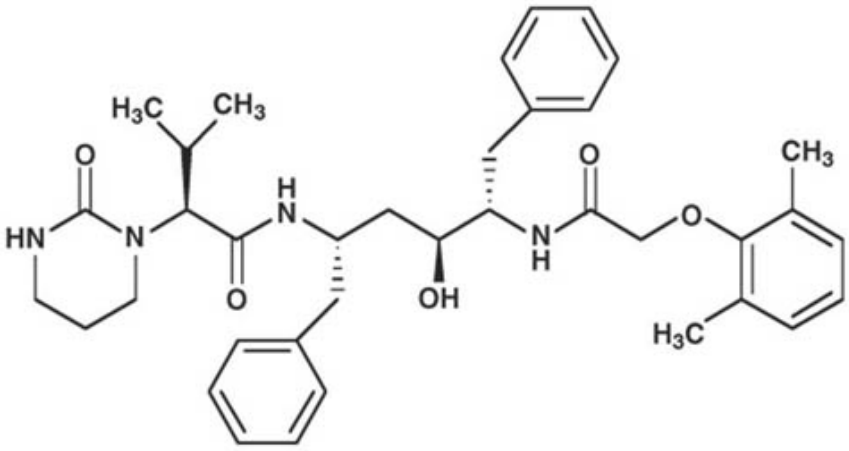
KALETRA oral solution contains 42.4% alcohol (v/v). Accidental ingestion of the product by a young child could result in significant alcohol-related toxicity and could approach the potential lethal dose of alcohol.

Human experience of acute overdosage with KALETRA is limited. Treatment of overdose with KALETRA should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with KALETRA. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Administration of activated charcoal may also be used to aid in removal of unabsorbed drug. Since KALETRA is highly protein bound, dialysis is unlikely to be beneficial in significant removal of the drug.

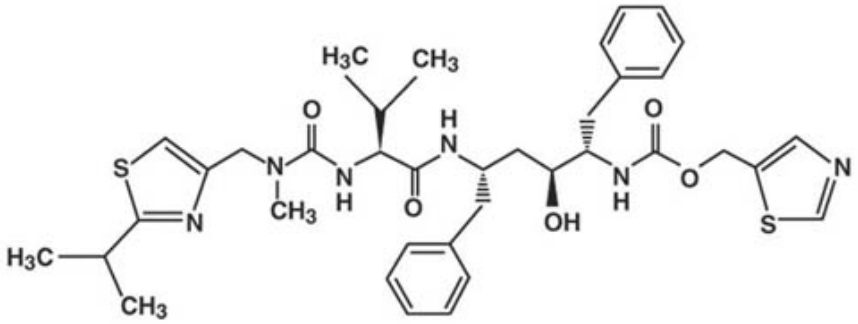
11 DESCRIPTION

KALETRA (lopinavir/ritonavir) is a co-formulation of lopinavir and ritonavir. Lopinavir is an inhibitor of the HIV-1 protease. As co-formulated in KALETRA, ritonavir inhibits the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

Lopinavir is chemically designated as [1*S*-[1*R**,(*R**), 3*R**, 4*R**]]-*N*-[4-[[(2,6-dimethylphenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2*H*)-pyrimidineacetamide. Its molecular formula is $C_{37}H_{48}N_4O_5$, and its molecular weight is 628.80. Lopinavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water. Lopinavir has the following structural formula:



Ritonavir is chemically designated as 10-hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5*S*-(5*R**,8*R**,10*R**,11*R**)]. Its molecular formula is $C_{37}H_{48}N_6O_5S_2$, and its molecular weight is 720.95. Ritonavir is a white to light tan powder. It is freely soluble in methanol and ethanol, soluble in isopropanol and practically insoluble in water. Ritonavir has the following structural formula:



KALETRA film-coated tablets are available for oral administration in two strengths:

- Yellow tablets containing 200 mg of lopinavir and 50 mg of ritonavir
- Pale yellow tablets containing 100 mg of lopinavir and 25 mg of ritonavir.

The yellow, 200 mg lopinavir/50 mg ritonavir, tablets contain the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, colloidal silicon dioxide, polyethylene glycol 3350, yellow ferric oxide E172, and polysorbate 80.

The pale yellow, 100 mg lopinavir/25 mg ritonavir, tablets contain the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The following are the ingredients in the film coating: polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol 3350, and yellow ferric oxide E172.

KALETRA oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural & artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

KALETRA oral solution contains 42.4% alcohol (v/v).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lopinavir is an antiviral drug *[See CLINICAL PHARMACOLOGY (12.4)]*.

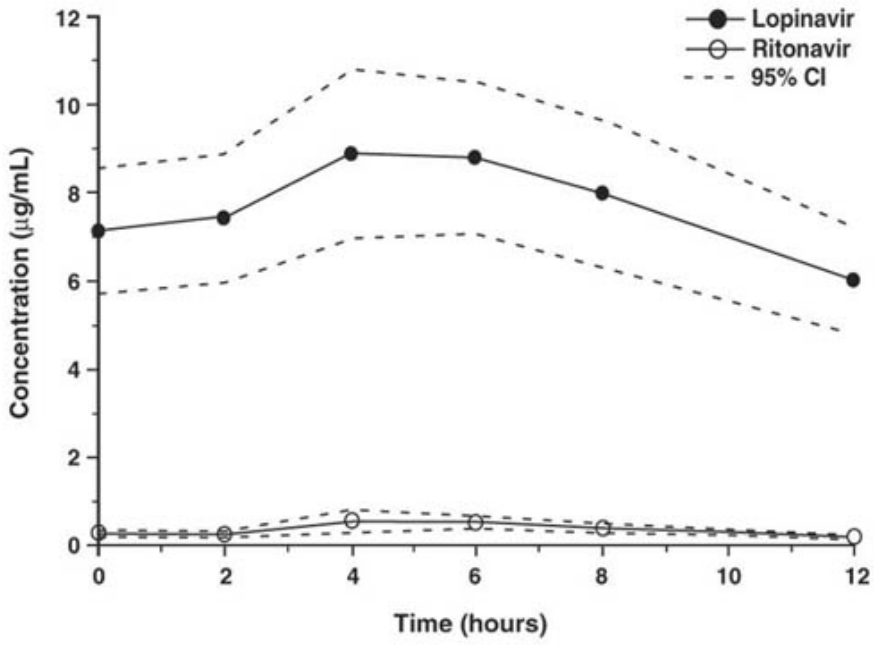
12.3 Pharmacokinetics

The pharmacokinetic properties of lopinavir co-administered with ritonavir have been evaluated in healthy adult volunteers and in HIV-1 infected patients; no substantial differences were observed between the two groups. Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma levels of lopinavir. Across studies, administration of KALETRA 400/100 mg twice-daily yields mean steady-state lopinavir plasma concentrations 15- to 20-fold higher than those of ritonavir in HIV-1 infected patients. The plasma levels of ritonavir are less than 7% of those obtained after the ritonavir dose of 600 mg twice-daily.

The *in vitro* antiviral EC_{50} of lopinavir is approximately 10-fold lower than that of ritonavir. Therefore, the antiviral activity of KALETRA is due to lopinavir.

Figure 1 displays the mean steady-state plasma concentrations of lopinavir and ritonavir after KALETRA 400/100 mg twice-daily with food for 3 weeks from a pharmacokinetic study in HIV-1 infected adult subjects (n = 19).

Figure 1. Mean Steady-state Plasma Concentrations with 95% Confidence Intervals (CI) for HIV-1 Infected Adult Subjects (N = 19)



Absorption

In a pharmacokinetic study in HIV-1 positive subjects (n = 19), multiple dosing with 400/100 mg KALETRA twice-daily with food for 3 weeks produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 9.8 ± 3.7 µg/mL, occurring approximately 4 hours after administration. The mean steady-state trough concentration prior to the morning dose was 7.1 ± 2.9 µg/mL and minimum concentration within a dosing interval was 5.5 ± 2.7 µg/mL. Lopinavir AUC over a 12 hour dosing interval averaged 92.6 ± 36.7 µg•h/mL. The absolute bioavailability of lopinavir co-formulated with ritonavir in humans has not been established. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of KALETRA co-formulated capsules and oral solution. When administered under fasting conditions, both the mean AUC and C_{max} of lopinavir were 22% lower for the KALETRA oral solution relative to the capsule formulation.

Plasma concentrations of lopinavir and ritonavir after administration of two 200/50 mg KALETRA tablets are similar to three 133.3/33.3 mg KALETRA capsules under fed conditions with less pharmacokinetic variability.

Effects of Food on Oral Absorption

KALETRA Tablets

No clinically significant changes in C_{max} and AUC were observed following administration of KALETRA tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of KALETRA tablets with a moderate fat meal (500 - 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 26.9% and 17.6%, respectively. Relative to fasting, administration of KALETRA tablets with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC by 18.9% but not C_{max}. Therefore, KALETRA tablets may be taken with or without food.

KALETRA Oral Solution

Relative to fasting, administration of KALETRA oral solution with a moderate fat meal (500 - 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 80 and 54%, respectively. Relative to fasting, administration of KALETRA oral solution with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC and C_{max} by 130% and 56%, respectively. To enhance bioavailability and minimize pharmacokinetic variability KALETRA oral solution should be taken with food.

Distribution

At steady state, lopinavir is approximately 98-99% bound to plasma proteins. Lopinavir binds to both alpha-1-acid glycoprotein (AAG) and albumin; however, it has a higher affinity for AAG. At steady state, lopinavir protein binding remains constant over the range of observed concentrations after 400/100 mg KALETRA twice-daily, and is similar between healthy volunteers and HIV-1 positive patients.

Metabolism

In vitro experiments with human hepatic microsomes indicate that lopinavir primarily undergoes oxidative metabolism. Lopinavir is extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by the CYP3A isozyme. Ritonavir is a potent CYP3A inhibitor which inhibits the metabolism of lopinavir, and therefore increases plasma levels of lopinavir. A ^{14}C-lopinavir study in humans showed that 89% of the plasma radioactivity after a single 400/100 mg KALETRA dose was due to parent drug. At least 13 lopinavir oxidative metabolites have been identified in man. Ritonavir has been shown to induce metabolic enzymes, resulting in the induction of its own metabolism. Pre-

dose lopinavir concentrations decline with time during multiple dosing, stabilizing after approximately 10 to 16 days.

Elimination

Following a 400/100 mg ^{14}C-lopinavir/ritonavir dose, approximately 10.4 ± 2.3% and 82.6 ± 2.5% of an administered dose of ^{14}C-lopinavir can be accounted for in urine and feces, respectively, after 8 days. Unchanged lopinavir accounted for approximately 2.2 and 19.8% of the administered dose in urine and feces, respectively. After multiple dosing, less than 3% of the lopinavir dose is excreted unchanged in the urine. The apparent oral clearance (CL/F) of lopinavir is 5.98 ± 5.75 L/hr (mean ± SD, n = 19).

Once-Daily Dosing

The pharmacokinetics of once-daily KALETRA have been evaluated in HIV-1 infected subjects naïve to antiretroviral treatment. KALETRA 800/200 mg was administered in combination with emtricitabine 200 mg and tenofovir DF 300 mg as part of a once-daily regimen. Multiple dosing of 800/200 mg KALETRA once-daily for 4 weeks with food (n = 24) produced a mean ± SD lopinavir peak plasma concentration (C_{max}) of 11.8 ± 3.7 µg/mL, occurring approximately 6 hours after administration. The mean steady-state lopinavir trough concentration prior to the morning dose was 3.2 ± 2.1 µg/mL and minimum concentration within a dosing interval was 1.7 ± 1.6 µg/mL. Lopinavir AUC over a 24 hour dosing interval averaged 154.1 ± 61.4 µg• h/mL.

Special Populations

Gender, Race and Age

No gender related pharmacokinetic differences have been observed in adult patients. No clinically important pharmacokinetic differences due to race have been identified. Lopinavir pharmacokinetics have not been studied in elderly patients.

Pediatric Patients

The pharmacokinetics of KALETRA oral solution 300/75 mg/m^2 twice-daily and 230/57.5 mg/m^2 twice-daily have been studied in a total of 53 pediatric patients in Study 940, ranging in age from 6 months to 12 years *[see CLINICAL STUDIES (14.4)]*. The 230/57.5 mg/m^2 twice-daily regimen without nevirapine and the 300/75 mg/m^2 twice-daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice-daily regimen (without nevirapine).

The mean steady-state lopinavir AUC, C_{max}, and C_{min} were 72.6 ± 31.1 µg•h/mL, 8.2 ± 2.9 and 3.4 ± 2.1 µg/mL, respectively after KALETRA oral solution 230/57.5 mg/m^2 twice-daily without nevirapine (n = 12), and were 85.8 ± 36.9 µg• h/mL, 10.0 ± 3.3 and 3.6 ± 3.5 µg/mL, respectively, after 300/75 mg/m^2 twice-daily with nevirapine (n = 12). The nevirapine regimen was 7 mg/kg twice-daily (6 months to 8 years) or 4 mg/kg twice-daily (> 8 years).

The pharmacokinetics of KALETRA oral solution at approximately 300/75 mg/m^2 twice-daily have also been evaluated in infants at approximately 6 weeks of age (n = 9) and between 6 weeks and 6 months of age (n = 18) in Study 1030. The mean steady-state lopinavir AUC_{12}, C_{max}, and C_{12} were 43.4 ± 14.8 µg• h/mL, 5.2 ± 1.8 µg/mL and 1.9 ± 1.1 µg/mL, respectively, in infants at approximately 6 weeks of age, and 74.5 ± 37.9 µg• h/mL, 9.4 ± 4.9 and 3.1 ± 1.8 µg/mL, respectively, in infants between 6 weeks and 6 months of age after KALETRA oral solution was administered at approximately 300/75 mg/m^2 twice-daily without concomitant NNRTI therapy.

The pharmacokinetics of KALETRA soft gelatin capsule and oral solution (Group 1: 400/100 mg/m^2 twice daily + 2 NRTIs; Group 2: 480/120 mg/m^2 twice daily + ≥ 1 NRTI + 1 NNRTI) have been evaluated in children and adolescents age ≥ 2 years to < 18 years of age who had failed prior therapy (n=26) in Study 1038. KALETRA doses of 400/100 and 480/120 mg/m^2 resulted in high lopinavir exposure, as almost all subjects had lopinavir AUC_{12} above 100 µg•h/mL. Both groups of subjects also achieved relatively high average minimum lopinavir concentrations.

KALETRA once-daily has not been evaluated in pediatric patients.

Renal Impairment

Lopinavir pharmacokinetics have not been studied in patients with renal impairment; however, since the renal clearance of lopinavir is negligible, a decrease in total body clearance is not expected in patients with renal impairment.

Hepatic Impairment

Lopinavir is principally metabolized and eliminated by the liver. Multiple dosing of KALETRA 400/100 mg twice-daily to HIV-1 and HCV co-infected patients with mild to moderate hepatic impairment (n = 12) resulted in a 30% increase in lopinavir AUC and 20% increase in C_{max} compared to HIV-1 infected subjects with normal hepatic function (n = 12). Additionally, the plasma protein binding of lopinavir was statistically significantly lower in both mild and moderate hepatic impairment compared to controls (99.09 vs. 99.31%, respectively). Caution should be exercised when administering KALETRA to subjects with hepatic impairment. KALETRA has not been studied in patients with

severe hepatic impairment *[See WARNINGS AND PRECAUTIONS (5.3) and USE IN SPECIFIC POPULATIONS (8.6)]*.

Drug Interactions

KALETRA is an inhibitor of the P450 isoform CYP3A *in vitro*. Co-administration of KALETRA and drugs primarily metabolized by CYP3A may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects *[See CONTRAINDICATIONS (4) and DRUG INTERACTIONS (7)]*.

KALETRA does not inhibit CYP2D6, CYP2C9, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations.

KALETRA has been shown *in vivo* to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to increase the clearance of lopinavir, resulting in lowered plasma concentrations of lopinavir. Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drug interaction studies were performed with KALETRA and other drugs likely to be co-administered and some drugs commonly used as probes for pharmacokinetic interactions. The effects of co-administration of KALETRA on the AUC, C_{max} and C_{min} are summarized in Table 10 (effect of other drugs on lopinavir) and Table 11 (effect of KALETRA on other drugs). The effects of other drugs on ritonavir are not shown since they generally correlate with those observed with lopinavir (if lopinavir concentrations are decreased, ritonavir concentrations are decreased) unless otherwise indicated in the table footnotes. For information regarding clinical recommendations, see Table 9 in *DRUG INTERACTIONS (7)*.

Table 10. Drug Interactions: Pharmacokinetic Parameters for Lopinavir in the Presence of the Co-administered Drug for Recommended Alterations in Dose or Regimen

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)		Ratio (in combination with co-administered drug/alone) of Lopinavir Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			n	C_{max}	AUC	C_{min}
Amprenavir	750 BID, 10 d	400/100 capsule BID, 21 d	12	0.72 (0.65, 0.79)	0.62 (0.56, 0.70)	0.43 (0.34, 0.56)

Efavirenz[1,10]	600 QHS, 9 d	400/100 capsule BID, 9 d	11, 7*	0.97 (0.78, 1.22)	0.81 (0.64, 1.03)	0.61 (0.38, 0.97)
	600 QHS, 9 d	500/125 tablet BID, 10 d	19	1.12 (1.02, 1.23)	1.06 (0.96, 1.17)	0.90 (0.78, 1.04)
	600 QHS, 9 d	600/150 tablet BID, 10 d	23	1.36 (1.28, 1.44)	1.36 (1.28, 1.44)	1.32 (1.21, 1.44)
Fosamprenavir[2]	700 BID plus ritonavir 100 BID, 14 d	400/100 capsule BID, 14 d	18	1.30 (0.85, 1.47)	1.37 (0.80, 1.55)	1.52 (0.72, 1.82)
Ketoconazole	200 single dose	400/100 capsule BID, 16 d	12	0.89 (0.80, 0.99)	0.87 (0.75, 1.00)	0.75 (0.55, 1.00)
Nelfinavir	1000 BID, 10 d	400/100 capsule BID, 21 d	13	0.79 (0.70, 0.89)	0.73 (0.63, 0.85)	0.62 (0.49, 0.78)
Nevirapine	200 BID, steady-state (> 1 yr)[3]	400/100 capsule BID, steady-state	22, 19*	0.81 (0.62, 1.05)	0.73 (0.53, 0.98)	0.49 (0.28, 0.74)
	7 mg/kg or 4 mg/kg QD, 2 wk; BID 1 wk[4]	(> 1 yr) 300/75 mg/m^2 oral solution BID, 3 wk	12, 15*	0.86 (0.64, 1.16)	0.78 (0.56, 1.09)	0.45 (0.25, 0.81)
Omeprazole	40 QD, 5 d	400/100 tablet BID, 10 d	12	1.08 (0.99, 1.17)	1.07 (0.99, 1.15)	1.03 (0.90, 1.18)
	40 QD, 5 d	800/200 tablet QD, 10 d	12	0.94 (0.88, 1.00)	0.92 (0.86, 0.99)	0.71 (0.57, 0.89)
Pravastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	0.98 (0.89, 1.08)	0.95 (0.85, 1.05)	0.88 (0.77, 1.02)
Rifabutin	150 QD, 10 d	400/100 capsule BID, 20 d	14	1.08 (0.97, 1.19)	1.17 (1.04, 1.31)	1.20 (0.96, 1.65)
Ranitidine	150 single dose	400/100 tablet BID, 10 d	12	0.99 (0.95, 1.03)	0.97 (0.93, 1.01)	0.90 (0.85, 0.95)
	150 single dose	800/200 tablet QD,	10	0.97	0.95	0.82

		10 d		(0.95, 1.00)	(0.91, 0.99)	(0.74, 0.91)
Rifampin	600 QD, 10 d	400/100 capsule BID, 20 d	22	0.45 (0.40, 0.51)	0.25 (0.21, 0.29)	0.01 (0.01, 0.02)
	600 QD, 14 d	800/200 capsule BID, 9 d[5]	10	1.02 (0.85, 1.23)	0.84 (0.64, 1.10)	0.43 (0.19, 0.96)
	600 QD, 14 d	400/400 capsule BID, 9 d[6]	9	0.93 (0.81, 1.07)	0.98 (0.81, 1.17)	1.03 (0.68, 1.56)
					Co-administration of KALETRA and rifampin is contraindicated. *[See CONTRAINDICATIONS (4)]*	
Ritonavir[3]	100 BID, 3-4 wk	400/100 capsule BID, 3-4 wk	8, 21*	1.28 (0.94, 1.76)	1.46 (1.04, 2.06)	2.16 (1.29, 3.62)
Tenofovir[7]	300 mg QD, 14 d	400/100 capsule BID, 14 d	24	NC†	NC†	NC†
Tipranavir/ritonavir[3]	500/200 mg BID(28 doses)	400/100 capsule BID(27 doses)	21 69	0.53 (0.40, 0.69)[8]	0.45 (0.32, 0.63)[8]	0.30 (0.17, 0.51)[8] 0.48 (0.40, 0.58)[9]

All interaction studies conducted in healthy, HIV-1 negative subjects unless otherwise indicated.

1 The pharmacokinetics of ritonavir are unaffected by concurrent efavirenz.

2 Data extracted from the fosamprenavir package insert.

3 Study conducted in HIV-1 positive adult subjects.

4 Study conducted in HIV-1 positive pediatric subjects ranging in age from 6 months to 12 years.

5 Titrated to 800/200 BID as 533/133 BID x 1 d, 667/167 BID x 1 d, then 800/200 BID x 7 d, compared to 400/100 BID x 10 days alone.

6 Titrated to 400/400 BID as 400/200 BID x 1 d, 400/300 BID x 1 d, then 400/400 BID x 7 d, compared to 400/100 BID x 10 days alone.

7 Data extracted from the tenofovir package insert.

8 Intensive PK analysis.

9 Drug levels obtained at 8-16 hrs post-dose.

10 Reference for comparison is lopinavir/ritonavir 400/100 mg BID without efavirenz

* Parallel group design; n for KALETRA + co-administered drug, n for KALETRA alone.

† NC = No change.

Table 11. Drug Interactions: Pharmacokinetic Parameters for co-administered Drug in the Presence of KALETRA for Recommended Alterations in Dose or Regimen

Co-administered Drug	Dose of Co-administered Drug (mg)	Dose of KALETRA (mg)		Ratio (in combination with KALETRA/alone) of co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00		
			n	C_{max}	AUC	C_{min}
Amprenavir[1]	750 BID, 10 d combo vs. 1200 BID, 14 d alone	400/100 capsule BID, 21 d	11	1.12 (0.91, 1.39)	1.72 (1.41, 2.09)	4.57 (3.51, 5.95)
Desipramine[2]	100 single dose	400/100 capsule BID, 10 d	15	0.91 (0.84, 0.97)	1.05 (0.96, 1.16)	N/A
Efavirenz	600 QHS, 9 d	400/100 capsule BID, 9 d	11, 12*	0.91 (0.72, 1.15)	0.84 (0.62, 1.15)	0.84 (0.58, 1.20)
Ethinyl Estradiol	35 µg QD, 21 d (Ortho Novum®)	400/100 capsule BID, 14 d	12	0.59 (0.52, 0.66)	0.58 (0.54, 0.62)	0.42 (0.36, 0.49)
Fosamprenavir[3]	700 BID plus ritonavir 100 BID, 14 d	400/100 capsule BID, 14 d	18	0.42 (0.30, 0.58)	0.37 (0.28, 0.49)	0.35 (0.27, 0.46)
Indinavir[1]	600 BID, 10 d combo nonfasting vs. 800 TID, 5 d alone fasting	400/100 capsule BID, 15 d	13	0.71 (0.63, 0.81)	0.91 (0.75, 1.10)	3.47 (2.60, 4.64)
Ketoconazole	200 single dose	400/100 capsule BID, 16 d	12	1.13 (0.91, 1.40)	3.04 (2.44, 3.79)	N/A
Methadone	5 single dose	400/100 capsule BID, 10 d	11	0.55 (0.48, 0.64)	0.47 (0.42, 0.53)	N/A
Nelfinavir[1]	1000 BID, 10 d combo vs. 1250 BID, 14 d alone	400/100 capsule BID, 21 d	13	0.93 (0.82, 1.05)	1.07 (0.95, 1.19)	1.86 (1.57, 2.22)
M8 metabolite				2.36 (1.91, 2.91)	3.46 (2.78, 4.31)	7.49 (5.85, 9.58)
Nevirapine	200 QD, 14 d; BID, 6 d	400/100 capsule BID, 20 d	5, 6*	1.05 (0.72, 1.52)	1.08 (0.72, 1.64)	1.15 (0.71, 1.86)
Norethindrone	1 QD, 21 d (Ortho	400/100	12	0.84	0.83	0.68

	Novum®)	capsule BID, 14 d		(0.75, 0.94)	(0.73, 0.94)	(0.54, 0.85)
Pravastatin	20 QD, 4 d	400/100 capsule BID, 14 d	12	1.26 (0.87, 1.83)	1.33 (0.91, 1.94)	N/A
Rifabutin	150 QD, 10 d; combo vs. 300 QD, 10 d; alone	400/100 capsule BID, 10 d	12	2.12 (1.89, 2.38)	3.03 (2.79, 3.30)	4.90 (3.18, 5.76)
25-*O*-desacetyl rifabutin				23.6 (13.7, 25.3)	47.5 (29.3, 51.8)	94.9 (74.0, 122)
Rifabutin + 25-*O*-desacetyl rifabutin[4]				3.46 (3.07, 3.91)	5.73 (5.08, 6.46)	9.53 (7.56, 12.01)
Rosuvastatin[5]	20 mg QD, 7 d	400/100 tablet BID, 7 d	15	4.66 (3.4, 6.4)	2.08 (1.66, 2.6)	1.04 (0.9, 1.2)
Tenofovir[6]	300 mg QD, 14 d	400/100 capsule BID, 14 d	24	NC†	1.32 (1.26, 1.38)	1.51 (1.32, 1.66)

All interaction studies conducted in healthy, HIV-1 negative subjects unless otherwise indicated.

1 Ratio of parameters for amprenavir, indinavir, and nelfinavir, are not normalized for dose.

2 Desipramine is a probe substrate for assessing effects on CYP2D6-mediated metabolism.

3 Data extracted from the fosamprenavir package insert.

4 Effect on the dose-normalized sum of rifabutin parent and 25-*O*-desacetyl rifabutin active metabolite.

5 Data extracted from the rosuvastatin package insert and results presented at the 2007 Conference on Retroviruses and Opportunistic Infection (*Hoody, et al, abstract L-107, poster #564*).

6 Data extracted from the tenofovir package insert.

* Parallel group design; n for KALETRA + co-administered drug, n for co-administered drug alone.

N/A = Not available.

† NC = No change.

12.4 Microbiology

Mechanism of Action

Lopinavir, an inhibitor of the HIV-1 protease, prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, non-infectious viral particles.

Antiviral Activity

The antiviral activity of lopinavir against laboratory HIV strains and clinical HIV-1 isolates was evaluated in acutely infected lymphoblastic cell lines and peripheral blood lymphocytes, respectively. In the absence of human serum, the mean 50% effective concentration (EC_{50}) values of lopinavir against five different HIV-1 subtype B laboratory strains ranged from 10-27 nM (0.006-0.017 µg/mL, 1 µg/mL = 1.6 µM) and ranged from 4-11 nM (0.003-0.007 µg/mL) against several HIV-1 subtype B clinical isolates (n = 6). In the presence of 50% human serum, the mean EC_{50} values of lopinavir against these five HIV-1 laboratory strains ranged from 65-289 nM (0.04-0.18 µg/mL), representing a 7- to 11-fold attenuation. Combination antiviral drug activity studies with lopinavir in cell cultures demonstrated additive to antagonistic activity with nelfinavir and additive to synergistic activity with amprenavir, atazanavir, indinavir, saquinavir and tipranavir. The EC_{50} values of lopinavir against three different HIV-2 strains ranged from 12-180 nM (0.008-113 µg/mL).

Resistance

HIV-1 isolates with reduced susceptibility to lopinavir have been selected in cell culture. The presence of ritonavir does not appear to influence the selection of lopinavir-resistant viruses in cell culture.

The selection of resistance to KALETRA in antiretroviral treatment naïve patients has not yet been characterized. In a study of 653 antiretroviral treatment naïve patients (Study 863), plasma viral isolates from each patient on treatment with plasma HIV-1 RNA > 400 copies/mL at Week 24, 32, 40 and/or 48 were analyzed. No evidence of resistance to KALETRA was observed in 37 evaluable KALETRA-treated patients (0%). Evidence of genotypic resistance to nelfinavir, defined as the presence of the D30N and/or L90M substitution in HIV-1 protease, was observed in 25/76 (33%) of evaluable nelfinavir-treated patients. The selection of resistance to KALETRA in antiretroviral treatment naïve pediatric patients (Study 940) appears to be consistent with that seen in adult patients (Study 863).

Resistance to KALETRA has been noted to emerge in patients treated with other protease inhibitors prior to KALETRA therapy. In studies of 227 antiretroviral treatment naïve and protease inhibitor experienced patients, isolates from 4 of 23 patients with quantifiable (> 400 copies/mL) viral RNA following treatment with KALETRA for 12 to 100 weeks displayed significantly reduced susceptibility to lopinavir compared to the corresponding baseline viral isolates. Three of these patients had previously received treatment with a single protease inhibitor (indinavir, nelfinavir, or saquinavir) and one patient had received treatment with multiple protease inhibitors (indinavir, ritonavir, and saquinavir). All four of these patients had at least 4 substitutions associated with protease inhibitor resistance immediately prior to KALETRA therapy. Following viral rebound, isolates from these

patients all contained additional substitutions, some of which are recognized to be associated with protease inhibitor resistance. However, there are insufficient data at this time to identify patterns of lopinavir-associated substitutions in isolates from patients on KALETRA therapy. The assessment of these patterns is under study.

Cross-resistance - Preclinical Studies

Varying degrees of cross-resistance have been observed among HIV-1 protease inhibitors. Little information is available on the cross-resistance of viruses that developed decreased susceptibility to lopinavir during KALETRA therapy.

The antiviral activity in cell culture of lopinavir against clinical isolates from patients previously treated with a single protease inhibitor was determined. Isolates that displayed > 4-fold reduced susceptibility to nelfinavir (n = 13) and saquinavir (n = 4), displayed < 4-fold reduced susceptibility to lopinavir. Isolates with > 4-fold reduced susceptibility to indinavir (n = 16) and ritonavir (n = 3) displayed a mean of 5.7- and 8.3-fold reduced susceptibility to lopinavir, respectively. Isolates from patients previously treated with two or more protease inhibitors showed greater reductions in susceptibility to lopinavir, as described in the following paragraph.

Clinical Studies - Antiviral Activity of KALETRA in Patients with Previous Protease Inhibitor Therapies

The clinical relevance of reduced susceptibility in cell culture to lopinavir has been examined by assessing the virologic response to KALETRA therapy in treatment-experienced patients, with respect to baseline viral genotype in three studies and baseline viral phenotype in one study.

Virologic response to KALETRA has been shown to be affected by the presence of three or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. Table 12 shows the 48-week virologic response (HIV-1 RNA <400 copies/mL) according to the number of the above protease inhibitor resistance mutations at baseline in studies 888 and 765 *[see CLINICAL STUDIES (14.2) and (14.3)]* and study 957 (see below).

Table 12. Virologic Response (HIV-1 RNA <400 copies/mL) at Week 48 by Baseline KALETRA Susceptibility and by Number of Protease Substitutions Associated with Reduced Response to KALETRA[1]

Number of protease inhibitor substitutions at baseline[1]	Study 888 (Single protease inhibitor-experienced[2], NNRTI-naïve) n=130	Study 765 (Single protease inhibitor-experienced[3], NNRTI-naïve) n=56	Study 957 (Multiple protease inhibitor-experienced[4], NNRTI-naïve) n=50

0-2	76/103 (74%)	34/45 (76%)	19/20 (95%)
3-5	13/26 (50%)	8/11 (73%)	18/26 (69%)
6 or more	0/1 (0%)	n/a	1/4 (25%)

1 Substitutions considered in the analysis included L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V.

2 43% indinavir, 42% nelfinavir, 10% ritonavir, 15% saquinavir.

3 41% indinavir, 38% nelfinavir, 4% ritonavir, 16% saquinavir.

4 86% indinavir, 54% nelfinavir, 80% ritonavir, 70% saquinavir.

Virologic response to KALETRA therapy with respect to phenotypic susceptibility to lopinavir at baseline was examined in Study 957. In this study 56 NNRTI-naïve patients with HIV-1 RNA >1,000 copies/mL despite previous therapy with at least two protease inhibitors selected from indinavir, nelfinavir, ritonavir, and saquinavir were randomized to receive one of two doses of KALETRA in combination with efavirenz and nucleoside reverse transcriptase inhibitors (NRTIs). The EC_{50} values of lopinavir against the 56 baseline viral isolates ranged from 0.5- to 96-fold the wild-type EC_{50} value. Fifty-five percent (31/56) of these baseline isolates displayed >4-fold reduced susceptibility to lopinavir. These 31 isolates had a median reduction in lopinavir susceptibility of 18-fold. Response to therapy by baseline lopinavir susceptibility is shown in Table 13.

Table 13. HIV-1 RNA Response at Week 48 by Baseline Lopinavir Susceptibility[1]

Lopinavir susceptibility[2] at baseline	HIV-1 RNA <400 copies/mL (%)	HIV-1 RNA <50 copies/mL (%)
< 10 fold	25/27 (93%)	22/27 (81%)
> 10 and < 40 fold	11/15 (73%)	9/15 (60%)
≥ 40 fold	2/8 (25%)	2/8 (25%)

1 Lopinavir susceptibility was determined by recombinant phenotypic technology performed by Virologic.

2 Fold change in susceptibility from wild type.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lopinavir/ritonavir combination was evaluated for carcinogenic potential by oral gavage administration to mice and rats for up to 104 weeks. Results showed an increase in the incidence of benign hepatocellular adenomas and an increase in the combined incidence of hepatocellular adenomas plus carcinoma in both males and females in mice and males in rats at doses that produced approximately 1.6-2.2 times (mice) and 0.5 times (rats) the human exposure (based on $AUC_{0\text{-}24hr}$ measurement) at the recommended dose of 400/100 mg KALETRA twice-daily. Administration of lopinavir/ritonavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats.

Carcinogenicity studies in mice and rats have been carried out on ritonavir. In male mice, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA twice-daily). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. There were no carcinogenic effects in rats. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA twice-daily regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation

assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg twice-daily).

14 CLINICAL STUDIES

14.1 Patients Without Prior Antiretroviral Therapy

Study 863: KALETRA twice-daily + stavudine + lamivudine compared to nelfinavir three-times-daily + stavudine + lamivudine

Study 863 was a randomized, double-blind, multicenter trial comparing treatment with KALETRA (400/100 mg twice-daily) plus stavudine and lamivudine versus nelfinavir (750 mg three-times-daily) plus stavudine and lamivudine in 653 antiretroviral treatment naïve patients. Patients had a mean age of 38 years (range: 19 to 84), 57% were Caucasian, and 80% were male. Mean baseline $CD4^+$ cell count was 259 cells/mm^3 (range: 2 to 949 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.9 log_{10} copies/mL (range: 2.6 to 6.8 log_{10} copies/mL).

Treatment response and outcomes of randomized treatment are presented in Table 14.

Table 14. Outcomes of Randomized Treatment Through Week 48 (Study 863)

Outcome	KALETRA+d4T+3TC (N = 326)	Nelfinavir+d4T+3TC (N = 327)
Responder[1]	75%	62%
Virologic failure[2]	9%	25%
Rebound	7%	15%
Never suppressed through Week 48	2%	9%
Death	2%	1%
Discontinued due to adverse events	4%	4%
Discontinued for other reasons[3]	10%	8%

1 Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.

2 Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.

3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons. Overall discontinuation through Week 48, including patients who discontinued subsequent to virologic failure, was 17% in the KALETRA arm and 24% in the nelfinavir arm.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the nelfinavir arm with HIV-1 RNA < 400 copies/mL (75% vs. 62%, respectively) and HIV-1 RNA < 50 copies/mL (67% vs. 52%, respectively). Treatment response by baseline HIV-1 RNA level subgroups is presented in Table 15.

Table 15. Proportion of Responders Through Week 48 by Baseline Viral Load (Study 863)

Baseline Viral Load (HIV-1 RNA copies/mL)	KALETRA +d4T+3TC			Nelfinavir +d4T+3TC		
	<400 copies/mL [1]	<50 copies/mL [2]	n	<400 copies/mL [1]	<50 copies/mL [2]	n
< 30,000	74%	71%	82	79%	72%	87
≥ 30,000 to < 100,000	81%	73%	79	67%	54%	79
≥ 100,000 to < 250,000	75%	64%	83	60%	47%	72
≥ 250,000	72%	60%	82	44%	33%	89

1 Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.

2 Patients achieved HIV-1 RNA < 50 copies/mL at Week 48.

Through 48 weeks of therapy, the mean increase from baseline in $CD4^+$ cell count was 207 cells/mm^3 for the KALETRA arm and 195 cells/mm^3 for the nelfinavir arm.

Study 418: KALETRA once-daily + tenofovir DF + emtricitabine compared to KALETRA twice-daily + tenofovir DF + emtricitabine

Study 418 was a randomized, open-label, multicenter trial comparing treatment with KALETRA 800/200 mg once-daily plus tenofovir DF and emtricitabine versus KALETRA 400/100 mg twice-daily plus tenofovir DF and emtricitabine in 190 antiretroviral treatment naïve patients. Patients had a mean age of 39 years (range: 19 to 75), 54% were Caucasian, and 78% were male. Mean baseline $CD4^+$ cell count was 260 cells/mm^3 (range: 3 to 1006 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.8 $\log_{10}$ copies/mL (range: 2.6 to 6.4 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment are presented in Table 16.

Table 16. Outcomes of Randomized Treatment Through Week 48 (Study 418)

Outcome	KALETRA QD + TDF + FTC (n = 115)	KALETRA BID + TDF + FTC (n = 75)
Responder[1]	71%	65%

Virologic failure[2]	10%	9%
Rebound	6%	5%
Never suppressed through Week 48	3%	4%
Death	0%	1%
Discontinued due to adverse events	12%	7%
Discontinued for other reasons[3]	7%	17%

1 Patients achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48.

2 Includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 48.

3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Through 48 weeks of therapy, 71% in the KALETRA once-daily arm and 65% in the KALETRA twice-daily arm achieved and maintained HIV-1 RNA < 50 copies/mL (95% confidence interval for the difference, -7.6% to 19.5%). Mean $CD4^+$cell count increases at Week 48 were 185 cells/mm^3 for the KALETRA once-daily arm and 196 cells/mm^3 for the KALETRA twice-daily arm.

14.2 Patients With Prior Antiretroviral Therapy

Study 888: KALETRA twice-daily + nevirapine + NRTIs compared to investigator-selected protease inhibitor(s) + nevirapine + NRTIs

Study 888 was a randomized, open-label, multicenter trial comparing treatment with KALETRA (400/100 mg twice-daily) plus nevirapine and nucleoside reverse transcriptase inhibitors versus investigator-selected protease inhibitor(s) plus nevirapine and nucleoside reverse transcriptase inhibitors in 288 single protease inhibitor-experienced, non-nucleoside reverse transcriptase inhibitor (NNRTI)-naïve patients. Patients had a mean age of 40 years (range: 18 to 74), 68% were Caucasian, and 86% were male. Mean baseline $CD4^+$cell count was 322 cells/mm^3 (range: 10 to 1059 cells/mm^3) and mean baseline plasma HIV-1 RNA was 4.1 $\log_{10}$ copies/mL (range: 2.6 to 6.0 $\log_{10}$ copies/mL).

Treatment response and outcomes of randomized treatment through Week 48 are presented in Table 17.

Table 17. Outcomes of Randomized Treatment Through Week 48 (Study 888)

Outcome	KALETRA + nevirapine + NRTIs (n = 148)	Investigator-Selected Protease Inhibitor(s) + nevirapine + NRTIs (n = 140)
Responder[1]	57%	33%

Virologic failure[2]	24%	41%
Rebound	11%	19%
Never suppressed through Week 48	13%	23%
Death	1%	2%
Discontinued due to adverse events	5%	11%
Discontinued for other reasons[3]	14%	13%

1 Patients achieved and maintained confirmed HIV-1 RNA < 400 copies/mL through Week 48.

2 Includes confirmed viral rebound and failure to achieve confirmed < 400 copies/mL through Week 48.

3 Includes lost to follow-up, patient's withdrawal, non-compliance, protocol violation and other reasons.

Through 48 weeks of therapy, there was a statistically significantly higher proportion of patients in the KALETRA arm compared to the investigator-selected protease inhibitor(s) arm with HIV-1 RNA < 400 copies/mL (57% vs. 33%, respectively).

Through 48 weeks of therapy, the mean increase from baseline in $CD4^+$ cell count was 111 cells/mm^3 for the KALETRA arm and 112 cells/mm^3 for the investigator-selected protease inhibitor(s) arm.

14.3 Other Studies Supporting Approval

Study 720: KALETRA twice-daily + stavudine + lamivudine
Study 765: KALETRA twice-daily + nevirapine + NRTIs

Study 720 (patients without prior antiretroviral therapy) and study 765 (patients with prior protease inhibitor therapy) were randomized, blinded, multi-center trials evaluating treatment with KALETRA at up to three dose levels (200/100 mg twice-daily [720 only], 400/100 mg twice-daily, and 400/200 mg twice-daily). In Study 720, all patients switched to 400/100 mg twice-daily between Weeks 48-72. Patients in study 720 had a mean age of 35 years, 70% were Caucasian, and 96% were male, while patients in study 765 had a mean age of 40 years, 73% were Caucasian, and 90% were male. Mean (range) baseline $CD4^+$ cell counts for patients in study 720 and study 765 were 338 (3-918) and 372 (72-807) cells/mm^3, respectively. Mean (range) baseline plasma HIV-1 RNA levels for patients in study 720 and study 765 were 4.9 (3.3 to 6.3) and 4.0 (2.9 to 5.8) $\log_{10}$ copies/mL, respectively.

Through 360 weeks of treatment in study 720, the proportion of patients with HIV-1 RNA < 400 (< 50) copies/mL was 61% (59%) [n = 100]. Among patients completing 360 weeks of treatment with $CD4^+$ cell count measurements [n=60], the mean (median) increase in $CD4^+$cell count was 501 (457)

cells/mm^3. Thirty-nine patients (39%) discontinued the study, including 13 (13%) discontinuations due to adverse reactions and 1 (1%) death.

Through 144 weeks of treatment in study 765, the proportion of patients with HIV-1 RNA < 400 (< 50) copies/mL was 54% (50%) [n = 70], and the corresponding mean increase in CD4$^+$cell count was 212 cells/mm^3. Twenty-seven patients (39%) discontinued the study, including 5 (7%) discontinuations secondary to adverse reactions and 2 (3%) deaths.

14.4 Pediatric Studies

Study 1030 was an open-label, multicenter, dose-finding trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL at a dose of 300/75 mg/m^2 twice daily plus 2 NRTIs in HIV-1 infected infants ≥14 days and <6 months of age.

Ten infants, ≥14 days and <6 wks of age, were enrolled at a median (range) age of 5.7 (3.6-6.0) weeks and all completed 24 weeks. At entry, median (range) HIV-1 RNA was 6.0 (4.7-7.2) $\log_{10}$ copies/mL. Seven of 10 infants had HIV-1 RNA <400 copies/mL at Week 24. At entry, median (range) CD4$^+$ percentage was 41 (16-59) with a median decrease of 1% (95% CI: -10, 18) from baseline to week 24 in 6 infants with available data.

Twenty-one infants, between 6 weeks and 6 months of age, were enrolled at a median (range) age of 14.7 (6.9-25.7) weeks and 19 of 21 infants completed 24 weeks. At entry, median (range) HIV RNA level was 5.8 (3.7-6.9) $\log_{10}$ copies/mL. Ten of 21 infants had HIV RNA <400 copies/mL at Week 24. At entry, the median (range) CD4$^+$ percentage was 32 (11-54) with a median increase of 4% (95% CI: -1, 9) from baseline to week 24 in 19 infants with available data.

See CLINICAL PHARMACOLOGY (12.3) for pharmacokinetic results.

Study 940 was an open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 100 antiretroviral naïve (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naïve. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m^2 or 300 mg lopinavir/75 mg ritonavir per m^2. Naïve patients also received lamivudine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m^2 dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline $CD4^+$ cell count was 838 cells/mm^3 and mean baseline plasma HIV-1 RNA was 4.7 $\log_{10}$ copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV-1 RNA < 400 copies/mL was 80% for antiretroviral naïve patients and 71% for antiretroviral experienced patients. The mean increase from baseline in $CD4^+$cell count was 404 cells/mm^3 for antiretroviral naïve and 284 cells/mm^3 for antiretroviral experienced patients treated through 48 weeks. At 48 weeks, two patients (2%) had prematurely discontinued the study. One antiretroviral naïve patient prematurely discontinued secondary to an adverse reaction, while one antiretroviral experienced patient prematurely discontinued secondary to an HIV-1 related event.

Dose selection in pediatric patients was based on the following:

- Among patients 14 days to 6 months of age receiving 300/75 mg/m^2 twice daily without nevirapine, plasma concentrations were lower than those observed in adults or in older children. This dose resulted in HIV-1 RNA < 400 copies/mL in 55% of patients (70% in those initiating treatment at <6 weeks of age).
- Among patients 6 months to 12 years of age, the 230/57.5 mg/m^2 oral solution twice daily regimen without nevirapine and the 300/75 mg/m^2 oral solution twice daily regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg twice daily regimen (without nevirapine). These doses resulted in treatment benefit (proportion of patients with HIV-1 RNA < 400 copies/mL) similar to that seen in the adult clinical trials.
- Among patients 12 to 18 years of age receiving 400/100 mg/m^2 or 480/120 mg/m^2 (with efavirenz) twice daily, plasma concentrations were 60-100% higher than among 6 to 12 year old patients receiving 230/57.5 mg/m^2. Mean apparent clearance was similar to that observed in adult patients receiving standard dose and in patients 6 to 12 years of age. Although changes in HIV-1 RNA in patients with prior treatment failure were less than anticipated, the pharmacokinetic data supports use of similar dosing as in patients 6 to 12 years of age, not to exceed the recommended adult dose.
- For all age groups, the body surface area dosing was converted to body weight dosing using the actual patient dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

KALETRA® (lopinavir/ritonavir) Film-Coated tablets and Oral Solution are available in the following strengths and package sizes:

16.1 KALETRA Tablets, 200 mg lopinavir/50 mg ritonavir

Yellow film-coated ovaloid tablets debossed with the corporate Abbott “A” logo and the Abbo-Code KA:

Bottles of 120 tablets …… (NDC 0074-6799-22)

Recommended Storage

Store KALETRA film-coated tablets at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59° to 86°F)[see USP controlled room temperature]. Dispense in original container or USP equivalent tight container (250 mL or less). For patient use: exposure of this product to high humidity outside the original container or USP equivalent tight container (250 mL or less) for longer than 2 weeks is not recommended.

16.2 KALETRA Tablets, 100 mg lopinavir/25 mg ritonavir

Pale yellow film-coated ovaloid tablets debossed with the corporate Abbott “A” logo and the Abbo-Code KC:

Bottles of 60 tablets …… (NDC 0074-0522-60)

Recommended Storage

Store KALETRA film-coated tablets at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59° to 86°F)[see USP controlled room temperature]. Dispense in original container or USP equivalent tight container (100 mL or less). For patient use: exposure of this product to high humidity outside the original container or USP equivalent tight container (100 mL or less) for longer than 2 weeks is not recommended.

16.3 KALETRA Oral Solution

KALETRA (lopinavir/ritonavir) oral solution is a light yellow to orange colored liquid supplied in amber-colored multiple-dose bottles containing 400 mg lopinavir/100 mg ritonavir per 5 mL (80 mg lopinavir/20 mg ritonavir per mL) packaged with a marked dosing cup in the following size:

160 mL bottle……..(NDC 0074-3956-46)

Recommended Storage

Store KALETRA oral solution at 2°-8°C (36°-46°F) until dispensed. Avoid exposure to excessive heat. For patient use, refrigerated KALETRA oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 25°C (77°F), oral solution should be used within 2 months.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2)

17.1 Information For Patients

- Patients and/or their care providers should pay special attention to accurate administration of their dose to minimize the risk of accidental overdose or underdose of KALETRA.
- Patients should be told that sustained decreases in plasma HIV-1 RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of KALETRA is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.
- Patients should be informed that KALETRA is not a cure for HIV-1 infection and that they may continue to develop opportunistic infections and other complications associated with HIV-1 disease. The long-term effects of KALETRA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with KALETRA can reduce the risk of transmitting HIV-1 to others through sexual contact.
- KALETRA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.
- KALETRA tablets can be taken at the same time as didanosine without food. Patients taking didanosine should take didanosine one hour before or two hours after KALETRA oral solution.

- Patients receiving sildenafil, tadalafil, or vardenafil should be advised that they may be at an increased risk of associated adverse reactions including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.
- Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with KALETRA.
- KALETRA tablets may be taken with or without food. KALETRA oral solution should be taken with food to enhance absorption.
- Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

Revised October 2008

17.2 FDA–Approved Patient Labeling

KALETRA®
(lopinavir/ritonavir) tablets
(lopinavir/ritonavir) oral solution

ALERT: Find out about medicines that should NOT be taken with KALETRA. Please also read the section "MEDICINES YOU SHOULD NOT TAKE WITH KALETRA."

Patient Information

KALETRA® (kuh-LEE-tra)

Generic Name: lopinavir/ritonavir (lop-IN-uh-veer/rit-ON-uh-veer)

Read this leaflet carefully before you start taking KALETRA. Also, read it each time you get your KALETRA prescription refilled, in case something has changed. This information does not take the place of talking with your doctor when you start this medicine and at check ups. Ask your doctor if you have any questions about KALETRA.

Before taking your medicine, make sure you have received the correct medicine. Compare the name above with the name on your bottle and the appearance of your medicine with the description provided below. Contact your pharmacist immediately if you believe a dispensing error has occurred.

What is KALETRA and how does it work?

KALETRA is a combination of two medicines. They are lopinavir and ritonavir. KALETRA is a type of medicine called an HIV-1 (human immunodeficiency virus) protease (PRO-tee-ase) inhibitor. KALETRA is always used in combination with other anti-HIV-1 medicines to treat people with human immunodeficiency virus (HIV-1) infection. KALETRA is for adults and for children age 14 days and older.

HIV-1 infection destroys $CD4^+$ (T) cells, which are important to the immune system. After a large number of T cells are destroyed, acquired immune deficiency syndrome (AIDS) develops.

KALETRA blocks HIV-1 protease, a chemical which is needed for HIV-1 to multiply. KALETRA reduces the amount of HIV-1 in your blood and increases the number of T cells. Reducing the amount of HIV-1 in the blood reduces the chance of death or infections that happen when your immune system is weak (opportunistic infections).

Does KALETRA cure HIV-1 or AIDS?

KALETRA does not cure HIV-1 infection or AIDS. The long-term effects of KALETRA are not known at this time. People taking KALETRA may still get opportunistic infections or other conditions that happen with HIV-1 infection. Some of these conditions are pneumonia, herpes virus infections, and *Mycobacterium avium* complex (MAC) infections.

Does KALETRA reduce the risk of passing HIV-1 to others?

KALETRA does not reduce the risk of passing HIV-1 to others through sexual contact or blood contamination. Continue to practice safe sex and do not use or share dirty needles.

How should I take KALETRA?

- You should stay under a doctor's care when taking KALETRA. Do not change your treatment or stop treatment without first talking with your doctor.
- You must take KALETRA every day exactly as your doctor prescribed it. The dose of KALETRA may be different for you than for other patients. Follow the directions from your doctor, exactly as written on the label.
- Dosing in adults: The usual KALETRA dose for adults is 400/100 mg (given as two yellow KALETRA tablets (200 mg lopinavir/ 50 mg ritonavir) or 5 mL of KALETRA oral solution) twice a day (morning and night), in combination with other anti-HIV-1 medicines.
  The doctor may prescribe a KALETRA dose of 800/200 mg (given as four yellow KALETRA tablets (200 mg lopinavir/ 50 mg ritonavir) or 10 mL of KALETRA oral solution) once-daily in

combination with other anti-HIV-1 medicines for some patients who have not taken anti-HIV-1 medications in the past.

- Dosing in children greater than 14 days of age:
  Children greater than 14 days of age can also take KALETRA. The child's doctor will decide the right dose based on the child's weight. KALETRA should not be administered once-daily in children.
- KALETRA tablets (all strengths) should be swallowed whole and not chewed, broken, or crushed.
- KALETRA tablets can be taken with or without food.
- When preparing a dose of KALETRA oral solution for your child, you should carefully measure the dose of KALETRA as instructed by your health care provider. This will reduce the possibility of giving too little or too much medicine which could reduce the effectiveness of therapy or cause serious harm to your child.
- Take KALETRA oral solution with food to help it work better.
- Do not change your dose or stop taking KALETRA without first talking with your doctor.
- When your KALETRA supply starts to run low, get more from your doctor or pharmacy. This is very important because the amount of virus in your blood may increase if the medicine is stopped for even a short time. The virus may develop resistance to KALETRA and become harder to treat.
- Be sure to set up a schedule and follow it carefully.
- Only take medicine that has been prescribed specifically for you. Do not give KALETRA to others or take medicine prescribed for someone else.

What should I do if I miss a dose of KALETRA?

It is important that you do not miss any doses. If you miss a dose of KALETRA, take it as soon as possible and then take your next scheduled dose at its regular time. If it is almost time for your next dose, do not take the missed dose. Wait and take the next dose at the regular time. Do not double the next dose.

What happens if I take too much KALETRA?

If you suspect that you took more than the prescribed dose of this medicine, contact your local poison control center or emergency room immediately.

As with all prescription medicines, KALETRA should be kept out of the reach of young children. KALETRA liquid contains a large amount of alcohol. If a toddler or young child accidentally drinks more than the recommended dose of KALETRA, it could make him/her sick from too much alcohol. Contact your local poison control center or emergency room immediately if this happens.

Who should not take KALETRA?

Together with your doctor, you need to decide whether KALETRA is right for you.

- Do not take KALETRA if you are taking certain medicines. These could cause serious side effects that could cause death. Before you take KALETRA, you must tell your doctor about all the medicines you are taking or are planning to take. These include other prescription and non-prescription medicines and herbal supplements.

For more information about medicines you should not take with KALETRA, please read the section titled "MEDICINES YOU SHOULD NOT TAKE WITH KALETRA."

- Do not take KALETRA if you have an allergy to KALETRA or any of its ingredients, including ritonavir or lopinavir.

Can I take KALETRA with other medications?*

KALETRA may interact with other medicines, including those you take without a prescription. You must tell your doctor about all the medicines you are taking or planning to take before you take KALETRA.

KALETRA can be taken with acid reducing agents (such as omeprazole and ranitidine) with no dose adjustment.

MEDICINES YOU SHOULD NOT TAKE WITH KALETRA:

- Do not take the following medicines with KALETRA because they can cause serious problems or death if taken with KALETRA.

- Dihydroergotamine, ergonovine, ergotamine and methylergonovine such as Cafergot®, Migranal® D.H.E. 45®, Ergotrate Maleate, Methergine, and others
- Halcion® (triazolam)
- Orap® (pimozide)
- Propulsid® (cisapride)
- Versed® (midazolam)

- Do not take KALETRA with rifampin, also known as Rimactane®, Rifadin®, Rifater®, or Rifamate®. Rifampin may lower the amount of KALETRA in your blood and make it less effective.
- Do not take KALETRA with St. John's wort (hypericum perforatum), an herbal product sold as a dietary supplement, or products containing St. John's wort. Talk with your doctor if you are taking or planning to take St. John's wort. Taking St. John's wort may decrease KALETRA levels and lead to increased viral load and possible resistance to KALETRA or cross-resistance to other anti-HIV-1 medicines.
- Do not take KALETRA with the cholesterol-lowering medicines Mevacor® (lovastatin) or Zocor® (simvastatin) because of possible serious reactions. There is also an increased risk of drug interactions between KALETRA and Lipitor® (atorvastatin) or Crestor® (rosuvastatin); talk to your doctor before you take any of these cholesterol-reducing medicines with KALETRA.

Medicines that require dosage adjustments:

It is possible that your doctor may need to increase or decrease the dose of other medicines when you are also taking KALETRA. Remember to tell your doctor all medicines you are taking or plan to take.

Before you take Viagra ® (sildenafil), Cialis® (tadalafil), or Levitra ® (vardenafil) with KALETRA, talk to your doctor about problems these two medicines can cause when taken together. You may get increased side effects of VIAGRA, CIALIS, or LEVITRA such as low blood pressure, vision changes, and penis erection lasting more than 4 hours. If an erection lasts longer than 4 hours, get medical help right away to avoid permanent damage to your penis. Your doctor can explain these symptoms to you.

- If you are taking oral contraceptives ("the pill") or the contraceptive patch to prevent pregnancy, you should use an additional or different type of contraception since KALETRA may reduce the effectiveness of oral or patch contraceptives.
- Efavirenz (Sustiva®), nevirapine (Viramune®), amprenavir (Agenerase®) and nelfinavir (Viracept®) may lower the amount of KALETRA in your blood. Your doctor may increase your dose of KALETRA if you are also taking efavirenz, nevirapine, amprenavir or nelfinavir. KALETRA should not be taken once-daily with these medicines.
- If you are taking Mycobutin® (rifabutin), your doctor will lower the dose of Mycobutin.
- A change in therapy should be considered if you are taking KALETRA with:

- Phenobarbital
- Phenytoin (Dilantin® and others)
- Carbamazepine (Tegretol® and others)

These medicines may lower the amount of KALETRA in your blood and make it less effective. KALETRA should not be taken once-daily with these medicines.

- If you are taking or before you begin using inhaled Flonase® (fluticasone propionate) talk to your doctor about problems these two medicines may cause when taken together. Your doctor may choose not to keep you on inhaled Flonase®.
- *Other Special Considerations*
  KALETRA oral solution contains alcohol. Talk with your doctor if you are taking or planning to take metronidazole or disulfiram. Severe nausea and vomiting can occur.
- *If you are taking both didanosine (Videx®) and KALETRA*
  Didanosine (Videx®) can be taken at the same time as KALETRA tablets without food. Didanosine (Videx®) should be taken one hour before or two hours after KALETRA oral solution.

What are the possible side effects of KALETRA?

- This list of side effects is not complete. If you have questions about side effects, ask your doctor, nurse, or pharmacist. You should report any new or continuing symptoms to your doctor right away. Your doctor may be able to help you manage these side effects.
- The most commonly reported side effects of moderate severity that are thought to be drug related are: abdominal pain, abnormal stools (bowel movements), diarrhea, feeling weak/tired, headache, and nausea. Children taking KALETRA may sometimes get a skin rash.
- Blood tests in patients taking KALETRA may show possible liver problems. People with liver disease such as Hepatitis B and Hepatitis C who take KALETRA may have worsening liver disease. Liver problems including death have occurred in patients taking KALETRA. In studies, it is unclear if KALETRA caused these liver problems because some patients had other illnesses or were taking other medicines.
- Some patients taking KALETRA can develop serious problems with their pancreas (pancreatitis), which may cause death. You have a higher chance of having pancreatitis if you have had it before. Tell your doctor if you have nausea, vomiting, or abdominal pain. These may be signs of pancreatitis.

- Some patients have large increases in triglycerides and cholesterol. The long-term chance of getting complications such as heart attacks or stroke due to increases in triglycerides and cholesterol caused by protease inhibitors is not known at this time.
- Diabetes and high blood sugar (hyperglycemia) occur in patients taking protease inhibitors such as KALETRA. Some patients have diabetes before starting protease inhibitors, others do not. Some patients need changes in their diabetes medicine. Others need new diabetes medicine.
- Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms and face may also happen. The cause and long term health effects of these conditions are not known at this time.
- Some patients with hemophilia have increased bleeding with protease inhibitors.
- There have been other side effects in patients taking KALETRA. However, these side effects may have been due to other medicines that patients were taking or to the illness itself. Some of these side effects can be serious.

What should I tell my doctor before taking KALETRA?

- *If you are pregnant or planning to become pregnant:* The effects of KALETRA on pregnant women or their unborn babies are not known.
- *If you are breast-feeding:* Do not breast-feed if you are taking KALETRA. You should not breast-feed if you have HIV-1. If you are a woman who has or will have a baby, talk with your doctor about the best way to feed your baby. You should be aware that if your baby does not already have HIV-1, there is a chance that HIV-1 can be transmitted through breast- feeding.
- *If you have liver problems:* If you have liver problems or are infected with Hepatitis B or Hepatitis C, you should tell your doctor before taking KALETRA.
- *If you have diabetes:* Some people taking protease inhibitors develop new or more serious diabetes or high blood sugar. Tell your doctor if you have diabetes or an increase in thirst or frequent urination.
- *If you have hemophilia:* Patients taking KALETRA may have increased bleeding.

How do I store KALETRA?

- Keep KALETRA and all other medicines out of the reach of children.

- KALETRA tablets should be stored at room temperature. Exposure of KALETRA tablets to high humidity outside the pharmacy container for longer than 2 weeks is not recommended.
- Refrigerated KALETRA oral solution remains stable until the expiration date printed on the label. If stored at room temperature up to 25°C (77°F), KALETRA oral solution should be used within 2 months.
- Avoid exposure to excessive heat.

Do not keep medicine that is out of date or that you no longer need. Be sure that if you throw any medicine away, it is out of the reach of children.

General advice about prescription medicines:

Talk to your doctor or other health care provider if you have any questions about this medicine or your condition. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have any concerns about this medicine, ask your doctor. Your doctor or pharmacist can give you information about this medicine that was written for health care professionals. Do not use this medicine for a condition for which it was not prescribed. Do not share this medicine with other people.

* The brands listed are trademarks of their respective owners and are not trademarks of Abbott Laboratories. The makers of these brands are not affiliated with and do not endorse Abbott Laboratories or its products.

Abbott Laboratories

North Chicago, IL 60064, U.S.A.

Rev. 6/2008